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# Contents

NUMBER 1, JULY, 1945

Bumby Paroxysmal Peritonitis	SILPPARD SHIGAI	1
Tissue Calcification and Renal Failure Produced by Massive Dose Vitamin D Therapy of Arthritis	T. S. DANOWSKI, A. W. WINKLER and J. P. PETERS	22
The Syndrome of Psors Myositis and Fibrositis, Its Manifestations and Its Significance in the Differential Diagnosis of Lower Abdominal Pain	JAMES A. GREENE	30
Aids in Physical Diagnosis: Signs over the Lower Left Lung Caused Chiefly by Cardiac Enlargement	EARL M. CHAPMAN and ROBIN G. ANDERSON	35
Diagnosis and Surgical Treatment of Ménière's Disease (Hydrops of Labyrinth).	KENNETH M. DAY	41
The Effect of Doryl (Carbaminoylecholine) in the Treatment of Peripheral Vascular Disease	GABRIEL SALAND, RANDOLPH ROSENTHAL, CHARLES KILIN and HERMAN ZURROW	48
The Integration of the Exact Sciences in Allergy Research	LESLIE N. GAY	53
The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both	HARRY L. ARNOLD, JR. and IRVIN L. TILDEN	65
A Current View of the Rabies Problem	J. CASATI	74
Case Reports		
Malaria Complicated by Pneumonia, Treatment with Sulfadiazine and Atabrine	Z. JAVIOR BIRCOVITZ	79
"Metastatic" Calcification in Soft Tissues of Legs in Osteitis Deformans	BERNARD SLIGMAN and LOUIS NATHANSON	82
Pulmonary Actinomycosis Due to <i>Actinomyces graminis</i> .	JOHN P. LYNCH and REBECCA A. HOLT	91
Mechanism of Reflex Anuria	GEORGE A. WOLF, JR.	99
Dextrocardia with Situs Inversus Complicated by Chronic Rheumatic Aortic and Mitral Endocarditis	GEORGE W. PARSON	102
Editorial		108
Reviews		111
College News Notes		113

## NUMBER 2, AUGUST, 1945

Penicillin in Suppurative Disease of the Lungs Due to <i>Streptococcus hemolyticus</i> HAROLD J F KULLMAN and JACOB ANTRIM CRELLIN	135
Upper Respiratory Infections A Résumé of Recent Pertinent Data and Observations of Incidence Aboard a Destroyer. WILLIAM H. HARRIS, JR	147
The Functional Consequences of Coronary Occlusion CARL J WIGGERS	158
Lymphocytosis in the Cerebrospinal Fluid IRVING L APPLEBAUM, JOEL SHRAGER and WILLIAM PAFF	170
Neuroses in the Combat Zone WILLIAM J BLECKWENN	177
Neuropsychiatric Complications Following Spinal Anesthesia H EDWARD YASKIN and BERNARD J ALPERS	184
Atrophic Arthritis Associated with Splenomegaly and Leukopenia FRANCIS N HATCH	201
Oliguria and Anuria Due to Increased Intrarenal Pressure JOHAN T PETERS	221
Case Reports	-
Thrombocytopenic Purpura Following the Use of Sulfathiazole PAUL S STRONG and EDWARD M GLASSBURN	237
Progressive (Disseminated) Coccidioidomycosis CHARLES D MARPLE	240
Familial Myasthenia Gravis LODOVICO MANCUSI-UNGARO	249
Acute Lupus Erythematosus Disseminatus A Report of a Case in a Male with Associated Atypical Verrucous Endocarditis (Libman-Sacks) S GILBERT BLOUNT, JR and JOHN T BARRETT	251
Comparative Electrocardiographic Changes in Angina Pectoris and Coronary Thrombosis in the Same Patient HAROLD H ROTHMILER	268
Equine Infectious Anemia Transmitted to Man JOHAN T PETERS	271
Editorial	275
Reviews	280
College News Notes	282

## NUMBER 3, SEPTEMBER, 1945

Acute Non-Specific Myocarditis SAMUEL CANDI and MARK C WHITLOCK	309
Meningococcal Meningitis Treated with Sulfadiazine and Sulfamerazine A Three-Year Study LEWIS K SWIFT, EDITH DUMOFF-STANLEY and HARVEY F. DOWLING	338

Coccidioidomycosis in Southern California: Report of a New Endemic Area with a Review of 100 Cases	JORRIST M. WILLITT and MAVIN WEISS	349
The Pathology of Sick Cell Disease	ROBERT C. MURPHY, JR. and SHEPARD SHAPIRO	376
The Diagnosis of Bacterial Heart Disease	MARION A. BLANKENHORN	398
The Treatment of Bronchiectasis with Chemotherapy and Allergy Management	J. WARRICK THOMAS, H. S. VAN ORDSRAND and C. TOMLINSON	405
Case Reports		
<i>Streptobacillus moniliformis</i> as a Cause of Subacute Bacterial Endocarditis. Report of a Case Treated with Penicillin	WALSH McDERMOTT, M. M. LEASK and M. BLNOIT	414
Primary Bronchopulmonary Aspergillosis, An Occupational Disease	GEORGE C. COI	423
Interlobar Effusion Associated with Congestive Heart Failure	S. BOHARAS and LEO H. CRISP	426
Hypertension Caused by Renal Infarction	S. BEN-ASHUR	431
Spontaneous Hemopneumothorax: Report of a Case Occurring in a Soldier	JOHN FRANKLIN	437
Multiple Fractures of Ribs by Cough	OSCAR SWINLFORD, JR. and JOHN MCKINNON	442
Editorial		445
Reviews		449
College News Notes		451

## NUMBER 4, OCTOBER, 1945

Treatment of Subacute Bacterial Endocarditis with Penicillin: Report of Cases Treated without Anticoagulant Agents	JESSAMINE R. GORMER, ARTHUR J. GEIGER and FRANCIS G. BLAKL	491
Endemic (Murine) Typhus Fever: Clinical Observations of 180 Cases	BYRON M. STUART and ROSCOE L. PULLEN	520
The Use of Thiouracil in the Treatment of Patients with Hyperthyroidism	J. L. GABRILOVE, M. J. KERT and L. J. SOFFER	537
Werner's Syndrome (Progeria of the Adult) and Rothmund's Syndrome, Two Types of Closely Related Heredofamilial Atrophic Dermatoses with Juvenile Cataracts and Endocrine Features, A Critical Study with Five New Cases	S. J. THANNHAUSER	559

Absorption and Excretion of Iron	ALEXANDER G LITTLE, JR, MAR- SCHELLE H POWER and E G WAKEFIELD	627
Ventricular Tachycardia—A Report of 10 Cases, Eight of Which Were Treated with Quinidine with Recovery in Seven	S L ZIMMERMAN	634
Case Reports		
Aneurysm of Aorta with Compression of Pulmonary Artery and Left Auricle	BERNARD B EICHLER and SIDNEY N HELLER	652
Case Report of Dissecting Aneurysm of the Aorta with Cardiac Tamponade	DAVID R SACKS	661
Splenic Neutropenia Report of a Case with Splenectomy	WANN LANGSTON, O A WHITE and J D ASHLEY, JR	667
A Syndrome Termed Reiter's Disease (Urethritis, Conjunctivitis and Arthritis)	C DUDLEY MILLER and DONALD W Mc- INTYRE	673
Editorial		683
Reviews		687
College News Notes		689

## NUMBER 5, NOVEMBER, 1945

Azotemia in Typhus Fever	A YEOMANS, J C SNYDER, E S MURRAY, R S ECKE and C J D ZARAFONETIS	711
Observations on the Treatment of Graves' Disease with Thiouracil	DAVID P BARR and EPHRAIM SHORR	754
Hyperophthalmopathic Graves' Disease	J H MEANS	779
The Effects of Thiouracil on the Thyroid Gland	JOHN WESLEY SHIRER and MORTIMER COHEN	790
Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, Penicillin and Repeated Thoracenteses	ALLEN I JOSEY, JOHN W TRINIS and WALTER F KAMMLER	800
The Early Diagnosis of Filariasis and Certain Suggestions Relative to Cause of Symptoms	W E LILDE and ALLEN I JOSEY	816
Studies of Filariasis in Soldiers Evacuated from the South Pacific	ABEL A GOODMAN, EMMANUEL M WEINBERGER, STUART W LIP- PINCOTT, ALLAN DI R MARBLE and WILLARD H WRIGHT	823
The Unusual in Gastrointestinal Roentgenology	G M TICL	837
Acute Infectious Polyneuritis (Guillain-Barré Type)	JOSEPH G CHUSID and GILBERT H MAPQUARDT	852

## Case Reports

- Isolated (Heidler's) Myocarditis Report of Case First Manifested by Arterial Emboli in Extremities and Terminally by Mural Thrombi in Three of the Heart Chambers. ROGER W. ROBINSON and FRANK B. QUINN 860

- The Combination of Hyperthyroidism and Pernicious Anemia Report of a Case with a Review of the Literature FELIX BOINSHRIM, DAVID SCHWIMMER and THOMAS HODGE McCAGACK 869

- Hemolytic Anemia, Hyperglobulinemia and Boeck's Sarcoid A R. CRANE and A. M. ZITLIN 882

- Editorial 890

- Reviews 893

- College News Notes 895

## NUMBER 6, DECEMBER, 1945

- Idiosyncratic Febrile Reactions to Thiouracil Clinical Characteristics and Possible Pharmacologic Significance JANET W. McARTHUR, RUFON W. RAWSON and J. H. MILANS 915

- Meningococcal Infections with Special Reference to Certain Diagnostic Considerations; An Analysis of Thirty-Seven Cases ABELT C. OSMAN and ISIDORE FISCHER 924

- Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria ROBERT C. MANCHESTER 935

- Infectious Mononucleosis A Clinical Study of Sixty-Three Cases ALFRED L. KRUGER, ABELT W. WALLACE and SAMUEL J. PENCHANSKY 945

- Broncholithiasis Report of 10 Cases J. ROBERT FOX and LOUIS H. CLIFF 955

- Amebiasis A Report of Thirty-Nine Cases Observed in an Army General Hospital Stationed in Northern Ireland JOHN N. EDSON, ALFRED P. INGEGNO and JOHN B. D'ALBORA 960

- Hypersensitivity and Rheumatic Fever Part I 969

- Part II Relation of Rheumatic Fever to Hypersensitivity JERRY K. AIKAWA 983

## Case Reports

- The Value of Penicillin in the Control of Sepsis Complicating a Case of Severe Granulocytopenia (Aleukemic Leukemia) VICTOR H. KUGEL and MAURICE A. SCHNITKER 1001

Back Pain as a Symptom of Carcinoma of the Body of the Pancreas EGON E KATTWINKEL	1006
Follicular Lymphoma (Brill-Symmers Disease) Unsuccessfully Treated with Penicillin NORMAN W. DREY and FRANK B QUEEN	1009
The Use of Penicillin in Agranulocytosis Case Report R W. MOODY and S KAUVAR	1015
Editorial	1018
Reviews	1023
College News Notes	1025
Index	1047

# ANNALS OF INTERNAL MEDICINE

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NUMBER 1

## BENIGN PAROXYSMAL PERITONITIS\*

By SHEPPARD SHUGAL, M.D. New York, N. Y.

The purpose of this paper is to describe in detail an unusual clinical syndrome which is at present little understood and often undiagnosed. The characteristics of this disorder are constant and distinctive.

The syndrome is characterized by recurrent paroxysms of severe abdominal pain with fever which may be as high as 105° F. Chilliness or a shaking chill may accompany the attacks. Involvement of the peritoneum is indicated by the subjective symptom of marked abdominal soreness and the objective finding of widespread, exquisite direct and rebound tenderness. On occasion true involuntary spasm of the abdominal wall may be noted. These abdominal signs are often so striking that to the surgeon they suggest an acute abdominal peritonitic lesion. Emergency operation has been repeatedly urged.

Chest pain of a pleuritic type is frequently present at some stage of the attack. Marked malaise, severe prostration, intense nausea and vomiting are almost constant characteristics. Diarrhea is conspicuously absent. Leukocytosis is a frequent finding. An occasional case may show urticarial wheals during the acute episode. This disease affects young people, often beginning in the second or third decade and continuing for many years. Nevertheless, they remain in good general health and their disorder, essentially benign, continues without the development of any persistent anatomical lesion and without permanent impairment of any physiologic function.

Although cases of an essentially similar nature have been previously described, emphasis has heretofore been laid upon the florid manifestations of erythema and purpura. This has tended to obscure the fundamental clinical picture of a disease which usually runs its course without skin eruption of any kind and with no bleeding tendency whatsoever. To draw attention to its distinctive clinical features, the term "benign paroxysmal peritonitis" is suggested until such time as classification becomes possible on a sound etiologic or pathologic basis.

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From the Medical Services, Mt Sinai Hospital, New York.



Included in this report are five new cases observed by the author. These are presented in clinical abstract and in table 1 as cases 1 to 5. In addition, data on five similar and probably related cases from the literature are tabulated in table 2 as cases 1 to 5. More detailed reference to two of these is made in the text.

### CASE REPORTS

*Case 1* A 38 year old white man stated that his illness began at the age of 13, with an attack of chest pain accompanied by fever of 104° F. From then until about the age of 27 such episodes recurred at intervals of one or two months. In each attack there was chest pain, often bilateral, worse on inspiration. Each episode was febrile, the patient being acutely ill, prostrated and incapacitated for from three to five days. Pleurisy or pleurodynia was diagnosed repeatedly. It is not certain that a friction rub was heard. Localized areas of chest wall tenderness were frequently noted.

From the age of 18, occasional attacks were associated with abdominal pain. At the age of 27 the abdominal pain became and remained the dominant feature in all attacks. At first generalized, it localized after some hours in the right lower quadrant. Marked direct right lower quadrant tenderness was present and the diagnosis of acute appendicitis was made repeatedly. Diffuse abdominal tenderness, both direct and rebound, was invariably noted, occasionally accompanied by definite spasm of the right rectus muscle. Nausea, vomiting, constipation and intense malaise were typical of these attacks. Chest pain might occur as the abdominal distress subsided. It was the occurrence of this "pleurisy" which convinced him of the essential identity of the two kinds of attacks and led him to refuse all offers of operation. During an attack a white blood cell count of 16,500 with 70 per cent polymorphonuclears was found. In none of the paroxysms were any skin lesions ever observed and there was never any evidence of gastrointestinal bleeding.

Neither the patient's past nor personal history shed any light upon the nature of his peculiar illness. He appeared to be well-adjusted, absorbed in his work and without overt neurotic trends. The family history was of interest only in that a maternal uncle had bronchial asthma. None of the patient's five siblings had had any allergic manifestation or any disease similar to that from which the patient suffered.

For more than nine years this patient's abdominal attacks continued, at intervals varying from two weeks to three months. In the intervals he remained quite well, except for occasional slight abdominal discomfort.

In an effort to ascertain the cause of his disease several complete investigations were made and the patient underwent a careful interval exploratory laparotomy. Complete roentgenographic studies of the gall-bladder, the gastrointestinal and genitourinary tracts were negative. Chest roentgenograms and an electrocardiogram were normal. Blood urea nitrogen was 17 mg per cent, glucose 75 mg, cholesterol 180 mg with ester fraction 120 mg, phosphorus 3.5 mg and calcium 9.9 mg. Heterophile antibody reaction was positive only in 1:8 dilution. Brucella agglutination was negative. Blood Wassermann reaction was negative. Sedimentation rate of red cells was normal during and between episodes. Interval blood count: hemoglobin 96 per cent, white blood cells 8,500, polymorphonuclears 66 per cent, lymphocytes 29, mononuclears 4, eosinophiles 1 per cent. Bromsulphalein test of liver function showed no retention in 30 minutes. Gastric secretion curve was normal. Stool and urine examinations were normal.

At the interval operation no lesion was found to account for the patient's attacks. Small bowel lesions, Meckel's diverticulum and mesenteric adenitis were especially sought for. An appendectomy was performed but despite this the patient's attacks continued unchanged.

TABLE I  
Benign Paroxysmal Peritonitis

Case No.	Age at Onset	Attack Duration Interval	Fever	Symptoms Signs	WBC Differential	Personal Family	AP-agar	Operation
1 38 M	13 (27)	3-5 days — 3-12 weeks	103- 101.5 F	RLQ pain Direct and rebound tenderness Spasm Chest pain	16,500 Pmn 70% Eos 0%	Negative — Negative Celiac asthma	Negative	Interval laparotomy, negative — Food trials negative to skin lesions
2 36 M	27	1-3 days — 1 week to 4 months	100- 102.6	RLQ, LLQ pain Direct and rebound tenderness Chest pain	19,000 Pmn 90% Eos 0%	Negative — Mother, sister Celiac allergy Celiac asthma	Liver, positive plurimium	Hypertrophy of visceral peritoneum Food trials negative — Excluded who the Previous appendectomy
3 18 M	13	2-4 days — 5 days to 2 weeks	102- 103	Generalized pain Direct and rebound tenderness Chest pain	18,000 Pmn 65% Eos 0%	Recurrent hives fever — Celiac hives fever	Recurrent and house dust four plus Food, plus minus	Appendectomy, Food trials negative No skin lesions
4 37 M	25	3-7 days — 1-6 months	103- 104	RLQ pain Direct and rebound tenderness Chest pain	12,700 Pmn 76% Eos 0% Interval Eos 0-7%	Negative Celiac hives fever — —	Fish two plus Other foods plus minus	No operation Partial food trial negative No skin lesions
5 38 M	18	1-3 days — 1 week to 6 months	102- 105	RLQ pain Direct and rebound tenderness Spasm Chest pain	13,250 Pmn 81% Eos 0% Interval Eos 0-9%	Negative — Negative —	Negative	No operation Partial food trial negative No skin lesions Recurrent febrile rheumatism

TABLE II  
Benign Parovysmal Peritonitis  
Similar Cases from the Literature

Case No. Age Sex	Age at Onset	Attack Duration Interval	Fever	Abdominal Symptoms Signs	WBC Differential	Allergy		Operation Food Trials Skin Lesions
						Personal Familial	Skin Tests	
1 26 M	2	1-2 days 1 week	103° F	Generalized pain, tenderness, left more than right, spasm	17,000- 27,000 Eos 0-24%	Pers H neg Family H neg Brother of Case 2	Scratch tests neg	Splenectomy Appendectomy Occasional purpura Cause undetermined
2 21 M	1	several days 1-6 weeks	103	Generalized pain, tenderness, spasm	15,000- 20,000 Eos 7%	Pers H neg Family H neg	N R	No operation Occasional petechiae Recurrent rheumatism Cause undetermined
3 29 M	22	several days 1-4 weeks	102.6	RUQ pain, tenderness, spasm	24,000 Eos 2%	Pers H neg Mother— hay fever	Foods neg	Appendectomy Erythema Cause undetermined
4 31 F	30	several days attacks "frequent"	100.4	Generalized pain, tenderness, spasm	11,500 Pmn nor- mal Eos 0%	Hay fever Family H not given	Wheat pos	Urticaria of skin and visceral peritoneum Improved with elimination of wheat
5 21 F	2 weeks	1-2 days 1-10 weeks	101	Generalized pain, tenderness, spasm	29,000 Eos 0%	Pers H neg Family H neg	Neg	Appendectomy Proved milk allergy No skin lesions

Thorough studies were made for a possible allergic cause of this patient's illness. Intracutaneous tests were essentially negative showing only suspiciously positive reactions to pepper and garlic. Greatly restricted trial diets had no influence upon his symptoms. A food diary yielded no information. Subcutaneous histamine given three times weekly in ascending dosage to the limits of tolerance over a period of several months was without observable effect. However, the patient appeared convinced that the use of ephedrine sulphate three times a day diminished the frequency of his attacks during the year preceding this report.

**CASE 2.** This was a 36 year old white man whose attacks of abdominal pain began at 27 and had occurred since then at intervals of one week to four months. In each attack there was severe usually cramplike pain and tenderness, both more marked in the lower part of the abdomen, nausea and vomiting, constipation, leukocytosis from 13,000-19,000 with 80-90 per cent polymorphs and fever varying from 100-102.5° F. On examination during the paroxysm rebound tenderness was usually striking, distention was slight, spincter absent. The acute phase of the attacks lasted from 12 to 24 hours, but it was two to three days before most of the abdominal tenderness and the prostration subsided. Localization of pain and tenderness was most often in the right lower quadrant though pain might begin in the left side of the abdomen.

After one year of illness the patient noticed the occurrence of chest pain of a pleuritic type which followed the major abdominal phase. Shift of tenderness from the lower abdomen to the right upper quadrant often with accompanying rib tenderness heralded the onset of this "chest stage." Referred shoulder pain and aggravation of pain upon inspiration or with the recumbent position were the usual accompaniments. No friction rub was heard.

With many of the abdominal attacks, and occasionally between them, discrete wheals were noted on the face or forehead. No generalized urticaria occurred. On one occasion, following severe vomiting, many tiny petechiae were seen in the eyelids. No gastrointestinal bleeding had ever been observed.

Between attacks the patient was usually completely well. However, minor abortive manifestations might occur, such as a sense of great exhaustion with abdominal crampiness and distention. At such times facial pallor and an urticarial wheal might be noted. These phenomena might presage a major episode or might pass off altogether after a few hours. The frequency of the attacks had not changed appreciably in recent years although they appeared somewhat less intense.

One year after the onset of his illness an exploratory laparotomy was performed during a mild attack with negative findings insofar as any gross lesion was concerned. But the surgeon noted that "The bowel lying in the lower abdomen and pelvis showed evidence of peritonitis manifested mainly by definite but moderate injection which involved equally the cecum, the ileum and the sigmoid. There was no exudate or fibrin."

The patient's past history included two brief episodes of dry pleurisy in early youth, chronic and recurring acute sinusitis, less severe in recent years, and acute appendicitis with appendectomy four years before onset of the present illness.

The family history was of particular interest. His sister had recurrent severe non-bloody diarrhea for five years. This was believed psychogenic until careful food trials discovered the existence of allergy to wheat, chocolate and coffee. Complete cure for the preceding six years followed exclusion of these foods. The patient's mother had known ever since childhood of a gastrointestinal reaction to uncooked apple. A maternal uncle had bronchial asthma.

Intradermal skin tests were negative and prolonged diet manipulations failed to demonstrate a specific food factor. The most stringent diets did not prevent the occurrence of attacks. The patient had undergone repeated investigations of every pertinent kind: roentgen-ray studies of the gastrointestinal and genitourinary tracts

and of the gall-bladder were negative. Roentgenograms of spine and chest were negative. Blood agglutinations for Brucella, typhoid and paratyphoid and for typhus fever were negative. Blood chemical studies, including urea nitrogen, glucose, calcium, phosphorus, sodium, potassium, and magnesium were within normal limits. Blood cholesterol was 370 mg. per cent. Interval blood counts were normal. Blood sedimentation rate during and after the attacks was normal.

Attempts to abort attacks with atienidin and ergotamine tartrate failed. Ephedrine sulphate taken regularly for several days did not prevent an acute attack. Nicotinic acid orally in 200 mg. dosage at two to three hour intervals appeared on one occasion to delay but did not prevent a paroxysm.

**Case 3** This was an 18 year old white male who in early childhood had an attack of severe pain in the right side of the chest and abdomen accompanied by fever. He was then well until the age of 13 when he had another similar attack lasting several days and he recalled that it was painful to move or walk. It was thought he might have had a gall-bladder attack. Six months later another attack occurred and then more and more frequently. Recently the interval between attacks had been only two weeks and for a short time they occurred every five days.

Description of an average episode is as follows: for almost a full day there was a prodromal period characterized by a sense of sluggishness and of being worn out. Pain appeared diffusely across the whole abdomen, often radiating into the flanks or even to the left shoulder. Pain might begin in either side of the abdomen. Nausea was usual but vomiting uncommon during the attacks. The temperature usually rose to 102° to 103° F. Abdominal tenderness, direct and rebound, was marked throughout the attack and for one or two days afterwards the abdomen was sore and walking painful. The duration of each episode was two to four days. In the preceding few years there was no chest pain at all. Leukocytosis as high as 18,000 had been present, but the polymorphonuclears numbered only 64 per cent. Eosinophilia was never observed. No skin eruption or bleeding tendency was ever noted. Between attacks, each of which was acute and completely disabling, this patient was altogether well.

One year before his admission to the Mt. Sinai Hospital an appendectomy was done, without thorough exploration. Ten days later the patient had one of his usual attacks and they continued to recur as before. Despite careful roentgen-ray investigation and blood studies, chemical, serologic and hematologic, nothing was found which offered a clue as to the cause of this patient's illness. Blood urea nitrogen, glucose, cholesterol, phosphatase, amylase, blood culture, bile culture, and spinal fluid studies were all within normal limits. Duodenal drainage was negative. Fragility of red blood cells was normal. Hemoglobin was 98 per cent, white blood cells 1,200, with normal differential. Blood sedimentation time (Linzenmeier technic) over two hours for 18 mm fall.

This patient had developed typical ragweed hay fever in the preceding two years. Skin testing showed four plus reactions to ragweed and to dust but food tests were negative other than one plus responses to grape, pineapple and cucumber. A paternal uncle had ragweed hay fever, the family background as to allergy being otherwise negative.

Repeated clinical testing with the suspected foods did not precipitate any abdominal attacks. Careful food diary, repeated trial diets and forced feedings failed to establish a definite relation between the ingestion of certain foods and the occurrence of the patient's attacks.

Unfortunately the patient lapsed from observation before the effect of any pharmacologic agents upon his attacks could be determined.

**Case 4** The patient was a 37 year old white male. For 12 years he had had recurrent episodes of fever, abdominal and chest pain, nausea and vomiting. During

this time he had had six hospital admissions, including a stay at the Mayo Clinic, in an effort to unravel the mystery of his disease. He had had practically every conceivable type of investigation which might have any bearing upon his disorder.

The patient's attacks generally followed this pattern. There was usually a prodromal period in which he felt some general malaise and a sense of being "let down." The attack itself began with epigastric or left upper quadrant pain, often cramplike in nature. This increased somewhat in severity and at the same time the patient felt chilly or might even have a shivering chill. His temperature rose usually to 103° or 104° F. The pain tended to shift toward the right upper quadrant where it finally localized. It was often noticeably aggravated by breathing and might then be accompanied by right shoulder pain. The patient was moderately prostrated and usually had to remain in bed three to six days.

Physical examination during the attack revealed quite marked right upper quadrant tenderness without definite spasm, at times slight tenderness over the lower ribs on the right both anteriorly and posteriorly. His signs had never been such as to suggest a need for urgent operation. Because of the localization of the patient's symptoms and signs in the right upper quadrant, the diagnosis of acute inflammation involving the gall-bladder or the right kidney had been made most often. However, several complete roentgen-ray studies of both gall-bladder and urinary tract were negative. On several occasions diaphragmatic pleurisy was suggested. No pulmonary signs were ever present. A pleuritic friction rub was not usually observed but, according to the patient, had been noted on one occasion.

Roentgenograms of the chest and complete gastrointestinal workup on several occasions were normal. Repeated blood cultures, urine cultures, stool cultures, and cultures of sinus washings revealed no significant organism. Numerous smears for malarial parasites and a variety of serologic reactions (Wassermann, heterophile, agglutination for typhoid, paratyphoid and Brucella, and Felix-Weil) were negative. Blood chemical studies including total protein determination were normal as were routine urine analyses and most blood counts. On one occasion during an attack the white cell count was 12,700 with 76 per cent polymorphonuclears. A single blood count while the patient was well showed 7 per cent eosinophilia. During this admission sternal marrow and muscle biopsy were both normal.

Because of the unusual character of the patient's illness and the difficulty in arriving at a satisfactory diagnosis he was suspected of a profound psychoneurosis or of being an outright malingerer. In the hospital he was closely observed while having his temperature taken and it was found that the temperature rises were genuine. In a recent evaluation of his personality by a competent psychiatrist, it was concluded that although he might have emotional difficulties it was extremely unlikely that psychogenic conflicts had any bearing on his illness.

In his personal, past and family history only the following appeared pertinent. In childhood he had had two or three episodes of pleurisy with fever. A maternal uncle had hay fever. From the allergic point of view, skin tests revealed only slight positive reaction to flounder, chocolate, pepper, onion, and tea. These skin reactions had no significance as judged by careful clinical trial. This patient, however, was not coöperative enough to exclude food allergy as a possible cause of his disease. The effect of adrenalin or other agents upon his attacks is not known.

It is an amazing fact that after 12 years of illness he was otherwise quite well. The only evidence of progression of his disease was that whereas at first his attacks occurred only two or three times a year, they had become monthly occurrences. Between attacks he might feel entirely well or he might be troubled by slight abdominal discomfort or malaise. He had lost no weight and had been able to carry on his job.

**Case 5** This was a 38 year old white man who at the age of 12 had had an

attack of abdominal pain diagnosed as acute appendicitis, with three recurrences yearly for three years thereafter. For an interval of three more years he was prone to repeated episodes of fatigue, nausea and a shaking chill without abdominal pain. From about the age of 18 to the time of admission, abdominal pain had again become the outstanding symptom. A typical paroxysm would begin gradually with a sense of pressure in the right lower quadrant, spreading over much of the abdomen. Tenderness and pain followed, which likewise usually started in the lower abdomen and spread upward. The pain remained severe for 18 to 24 hours, but general abdominal soreness persisted for two to three days after the acute stage had passed. The temperature often rose as high as 102-103° F, and might even reach 105° F. The febrile stage did not usually last longer than 24 hours. Nausea was frequent, vomiting occasional. Diarrhea was consistently absent, the bowels being constipated or regular. The patient was usually confined to bed for one or two days. During the attack there was usually a sharp loss of weight. The patient had never at any time observed skin lesions of any type or bleeding tendency of any kind.

Ten years previously the frequency of the attacks increased to every two months and more recently they became still more frequent so that in the preceding 12 months the patient had had 22 major paroxysms. As a result the free interval was often only eight days. The longest interval had been six months, which occurred six years ago. Despite the intensity of the paroxysms and their increasing frequency, the patient felt well and vigorous, retained a good appetite, maintained his weight and, though handicapped, was able to carry on his business actively.

In one out of every five attacks the pain localized ultimately in the right upper quadrant and took on a pleuritic character, being distinctly aggravated by breathing. Pain in the right shoulder might then be present. Because of the sharpness of the pleuritic type of pain the patient was unable to lie down or sleep. This syndrome might last three days.

The physical findings during an attack, or shortly after, are described in the following note taken from the report of the Consultation Service at Mt. Sinai Hospital: "The patient had an attack of pain in the right upper quadrant and lower right chest last night. The pain was more marked on inspiration. His temperature was 100° F (p.o.). Physical examination reveals rigidity and tenderness in the right upper quadrant. Jarring of the chest causes pain in the right upper quadrant. There was also slight rigidity of the right lower quadrant. Fluoroscopy showed both leaves of the diaphragm to move well.

"The negative gall-bladder roentgen-ray, the history of previous attacks beginning with pain across the lower quadrants and shifting after 24 hours to the upper abdomen and accompanied by nausea and fever suggest that the attacks were caused by recurrent appendicitis. The presence of abnormal signs in the right upper quadrant suggests that we are dealing with an infrahepatic inflammatory process which is best explained on the basis of an appendicitis with the appendix situated high in the abdomen."

The surgical consultant agreed with the above opinion and advised exploratory laparotomy.

It is evident that the acuteness of the abdominal findings during this patient's paroxysms was such as to simulate closely an acute surgical abdomen. He refused operation and at the time of this report he had not been explored either in a free interval or during an attack.

In 1936, 1937, 1938, 1939, 1940 and again in 1944 the patient had repeated roentgenographic and other studies. Gastrointestinal series, cholecystogram, barium enema, intravenous pyelogram and flat plates of chest and abdomen were all negative. Basal metabolic rate was - 3 per cent. Electrocardiogram was normal. Blood Kahn reaction and agglutination tests against brucella were negative. Blood non-protein





than 24 hours The relationship of fatigue, exertion, worry and other overt psychological factors to the attacks is debatable

2 *Abdominal and Chest Pain* Abdominal pain is one of the essential symptoms At first it may be diffuse and cramplike or on the other hand it may be localized in the upper or lower abdomen with a steady and gnawing character Localization is prone to occur in the right side of the abdomen, especially in the right lower quadrant, as in four of the five cases Abdominal soreness rather than actual pain may sometimes be the first indication of an attack, preceding the occurrence of actual pain When the upper abdomen is involved, the pain often takes on a pleuritic character and is accompanied by pain in the shoulder, thus suggesting diaphragmatic irritation In three cases (1, 2, 5) lower abdominal tenderness spread upward in occasional attacks and led to a chest phase almost distinct from the first or abdominal stage At these times marked chest wall tenderness was elicited No friction rub or pulmonary signs were audible

In case 1 recurrent "pleurisy" was present for years before abdominal pain appeared as the primary symptom These paroxysms of chest pain were accompanied by fever rising to 103 or 104° F After 14 years the patient became subject to bouts of abdominal pain with a syndrome identical with the other cases

3 *Fever* Fever is characteristic of the disease On rare occasions an attack may be afebrile, but some fever is an almost invariable accompaniment Most often there is an abrupt rise to 102° or 103° F, but the temperature may even reach 105° F and with a shaking chill Occasionally the febrile paroxysms may be the predominating clinical feature and the patient be closely studied as a case of "fever of unknown origin" (case 4) The duration of the fever is usually not more than 24 to 36 hours A slight secondary rise may accompany the 'chest phase' as in cases 1, 2 and 5

4 *Abdominal Signs* Marked direct and rebound tenderness are characteristic of the acute abdominal crises They are indicative of the underlying peritoneal irritation At first localized and most often in the lower abdomen, these signs become almost generalized throughout the abdomen Some abdominal soreness persists for two to three days The patient often walks in a typically stooped posture to relax tension upon the tender abdomen This may be noticeable at the very beginning of an acute episode Distinct spasm of the abdominal wall has been noted at times in two of the cases, 1 and 5, thus completing the picture of a "surgical abdomen" It was absent in the other cases Moderate abdominal distention may be present

5 *Systemic and Gastrointestinal Manifestations* Marked prostration and malaise characterize the acute phase A sense of profound exhaustion may precede the actual onset, or may be the chief symptom of an abortive episode in association with abdominal crampiness and distention General muscle achiness and actual muscle soreness may follow an attack



of no clinical significance. In case 3 marked reactions to ragweed and house dust were present and were of significance for the patient's nasal symptoms.

Careful investigation by means of trial and addition diets in cases 1, 2 and 3, failed to reveal causative food factors. In cases 4 and 5 this was still to be carried out in an exhaustive manner, though elimination diets yielded no information in case 5.

*9 Operative Findings.* In only one of the five cases (case 2) was laparotomy performed during an acute paroxysm. In this instance the sole finding was definite injection of subserosal vessels of the visceral peritoneum in the lower abdominal cavity. In this case appendectomy had been performed for acute appendicitis four years before the onset of the present illness. In two other cases (1 and 3) appendectomy did not affect the course of this disease. Careful interval exploration in case 1 revealed no intra-abdominal lesion whatsoever. No laparotomy was done in cases 4 and 5.

#### PATHOLOGY AND ETIOLOGY

The clinical characteristics of this syndrome offer a clue to its fundamental pathologic mechanism. It may be fairly assumed from its prolonged course punctuated by febrile paroxysms that the essential lesion consists of some form of acute readily reversible inflammatory reaction. Certain observations indicate more precisely the probable nature of this reaction. Thus, the association of urticarial wheals with the attacks in case 2, together with the operative finding in the same case of hyperemia of the visceral peritoneum in the lower abdomen point to a vascular response of dilatation and hyperpermeability.

From the available clinical evidence the site of this vascular reaction may also be postulated. The outstanding physical findings are those of marked peritoneal irritation, which coincides with such operative findings as are at present available. Thus, the tissue reaction which gives this disease its distinctive clinical character takes place in the visceral peritoneum. Whether this is the primary site of reaction or whether it is secondary to an intestinal mucous membrane response cannot be stated. An enteritis alone would not produce the marked direct and rebound tenderness which are invariably present. Furthermore, diarrhea would be an expected symptom and this is invariably absent during the typical paroxysm.

Although the disease may well be enteric in origin, it might be conceived of as an unusual form of recurrent acute serositis. The history of paroxysmal chest pain in case 1 which preceded the abdominal syndrome by several years, and the unusual rheumatism in case 5 suggest that the pathologic process may involve other serous membranes as well as the peritoneum.

The suggestion that this syndrome has its basis in a form of vascular disease prompts speculation as to its possible relation to other systemic vascular disorders. Attention logically focuses first upon the "Erythema

Group" of Osler within whose broad category at least one case similar to those in the present series may be found. Thus, in Osler's very first paper on the visceral complications of the erythema group,<sup>1</sup> case 1 possesses many of the ear-marks of this syndrome—a man of 27 who for eight years had attacks of severe abdominal pain, vomiting and fever followed by abdominal soreness. Skin erythema, a prominent finding at first, was absent in the last two years of observation. All diagnostic procedures then available were negative.

Again in a later paper<sup>2</sup> Osler notes with respect to the gastrointestinal symptoms of visceral erythema that "the manifestations may be for years abdominal without skin eruptions." On the other hand it should be noted that within the "Erythema Group" are included cases characterized by gross hemorrhage from the kidneys and gastrointestinal tract, by termination in uremia, or by endocarditis, pericarditis and an ultimately fatal, febrile course. Such clinical phenomena appear altogether foreign to the syndrome here described. More recent clinical contributions to the study of the visceral manifestations of cutaneous erythema fail to shed light upon the present problem.<sup>3,4</sup> It may be suggested that just as other diseases, notably acute lupus erythematosus, have been split off from the general category of Osler's erythema, so too this disorder now warrants separate classification.

The association of abdominal pain with angioneurotic edema, particularly of the familial type, was likewise given particular emphasis by Osler.<sup>5</sup> Single episodes of great severity and simulating acute intestinal obstruction have been described.<sup>6</sup> However, the occurrence in the course of angioneurotic edema of a syndrome of the type here described has not been reported.

Abdominal pain is a primary characteristic of Henoch's purpura.<sup>7</sup> In most case reports isolated acute attacks of considerable violence are reported, which simulate an acutely inflamed abdomen,<sup>8</sup> but evidence of gross gastrointestinal bleeding is usually present,<sup>9</sup> and actual cutaneous purpura occurs, though it may be delayed. Renal involvement, a frequent characteristic of Henoch's purpura which often leads to a fatal issue, likewise distinguishes that disease from the present syndrome.

As with other varieties of the "Erythema Group" Henoch's purpura includes certain cases of a milder type which tend to be of prolonged duration with repeated attacks. In such cases the element of purpura may be so slight as to raise the question whether one is dealing with the same disease. Evidence of visceral bleeding is likely to be absent altogether. Althausen, Deamer and Kerr,<sup>10</sup> in an excellent paper, "The False Acute Abdomen: Henoch's Purpura and Abdominal Allergy," have described several such instances. The clinical features of four of these are of the greatest interest for an understanding of the present syndrome. They are included as cases 1 to 4 in table 2. Three of these closely approximate the clinical picture of the disease here designated as benign paroxysmal peritonitis. They are

characterized by recurrent attacks over many years of severe abdominal pain and tenderness with high fever and leukocytosis. In two instances the paroxysms had continued for 20 and 24 years ever since onset in very early childhood. These two patients were brothers. In the third case the duration was seven years at the time of publication.

The first two cases exhibited rather mild cutaneous purpura on a few occasions but otherwise the attacks were without skin eruption. In case 3 erythema was a frequent accompaniment of the acute episodes, but no purpura occurred. Interval eosinophilia was present at times in cases 1 and 2 just as has been observed in cases 4 and 5 of the author's series. Marked leukocytosis and polynucleosis were characteristic of the acute attack in each of these cases. In contrast with the present group, however, spasm of the abdominal wall appears to have been a striking finding.

Another interesting parallel is offered by the second case in which recurrent pain in the ankles and knees, occasionally with redness, was present between 11 and 20 years of age. This resembles the similar syndrome in case 5 of the author's group. In neither case was there any direct relation between these attacks and those affecting the abdomen but the Henoch-Schoenlein pattern is evident and it appears probable that this peculiar form of rheumatism is another manifestation of the same underlying disorder.

In none of these three cases which parallel the present syndrome most closely was it possible to establish any definite cause or to influence the general course of the disease. The fourth case, taken from the same paper, presents a syndrome very similar to the one under discussion. However, this patient's disease was of a comparatively short duration. A temperature rise was apparently noted on but one occasion. The operative finding of urticaria of the visceral peritoneum makes this a case of particular interest.

*Case 4 (table 2)* A woman of 31 had suffered from childhood to the age of 14 from recurrent attacks of abdominal pain and vomiting. All her life she had been subject to urticaria, hay fever and hemorrhagic manifestations such as petechiae, bleeding from the gums, epistaxis and profuse bleeding from small cuts.

At the age of 30 the patient had an attack of severe epigastric pain, radiating to the back, with nausea, profuse salivation and drenching perspiration. The pain lasted several hours. Nausea and upper abdominal tenderness persisted for several days. Blood, urine, cholecystography and gastrointestinal series were all negative.

Six months before admission the patient began to have frequent similar though less severe episodes. For a while tincture of belladonna appeared to be of some value and atropine gave spectacular but temporary relief during an attack. Physical examination revealed marked abdominal hyperesthesia, general abdominal tenderness and rigidity, all more on the right side. Temperature was 100.4° F, white blood cells 11,500, normal differential. Exploration of the abdomen disclosed small whitish papules on the visceral peritoneum, especially numerous over the appendix. Appendectomy was performed. Microscopic examination showed edema of the subserosal tissue. The attacks continued until later skin testing revealed sensitivity to several foods including wheat. With elimination of wheat products, the attacks have occurred only rarely and in a mild form.

This case differs from those of the author's series in having positive skin

reactions to foods, at least one of which was of apparent clinical significance. The marked improvement which evidently followed exclusion of the offending food factor warrants the conclusion that in this instance the abdominal syndrome was due to food allergy. Further consideration of abdominal allergy due to foods in relation to benign paroxysmal peritonitis is warranted in the light of these observations.

Gastrointestinal reactions due to food hypersensitiveness may be of acute or chronic types. The acute reactions are usually characterized by severe colic, nausea, vomiting and diarrhea. Often there is urticaria or angio-neurotic edema as well. Such manifestations first described as forms of egg poisoning<sup>11, 12</sup> were also graphically presented in 1909 as a form of "Buckwheat Poisoning"<sup>13</sup>. Despite the title, early experiments with skin testing are included, which revealed the exquisite skin hypersensitiveness to the specific food allergen which is typical of the acute, immediate gastrointestinal reaction. Additional cases with similar symptomatology have been described repeatedly<sup>14, 15, 16, 17</sup>. More violent reactions characterized by vasomotor collapse and even death have been observed<sup>18</sup>.

Purpura, clearly due to food allergy, has been described by Alexander and Eierman<sup>19, 20</sup> and also by Kahn<sup>21</sup>. In some of these cases abdominal pain was present, but none of them presented the clinical picture with which this paper is concerned. The presence of fever and marked abdominal tenderness, direct and rebound, constitute essential characteristics of this disorder. Few reported instances of food allergy include these phenomena. In this connection Rowe<sup>25</sup> states "The fact that acute allergy may produce fever as well as leukocytosis must be kept in mind in differential diagnosis. Eosinophilia moreover is not necessarily present in allergy." He also cites a case illustrating the occurrence of fever and acute abdominal findings apparently as an allergic response to a specific food.

"A man of 39 with increasing pain in the right side of the abdomen, particularly right upper quadrant for 15 years. Distention, belching, canker sore, coated tongue. Appendectomy without results six years before. Spastic constipation and diarrhea.

"Three years ago sudden severe left lower quadrant pain, great tenderness, increasing fever, leukocytosis indicating emergency operation. Diffuse congestion of intestinal coils in lower abdomen with considerable gray sterile fluid.

"Later, idiosyncrasy to crab found responsible for similar though milder attacks. Gastrointestinal series, barium enema, stools, neg. Well for two years with elimination of several foods. Skin tests neg."

The operative findings in this case are reminiscent of those in case 2 of the present series and the clinical picture is similar. Because of the relative paucity of precise clinical data this case is not included in table 2.

As further support of his contention that fever may constitute an allergic reaction to food, Rowe quotes a colleague "who observed a patient in whom sensitization to milk produces a temperature of 105° F." He also cites a case of a lad of 19 with recurrent attacks of fever from 101 to 105° F. for several days every two to three months for 12 years. He became entirely well while under observation for more than two years on a milk-free diet.

Additional evidence for the occurrence of fever in allergic reactions to food may be derived from a report by Carr<sup>22</sup> in which there is rather briefly noted the development of fever as high as 102.4° F, together with headache, drowsiness and joint pains when a man of 35 was placed on a Sippy régime for duodenal ulcer. The symptoms subsided when the patient was taken off milk but the experiment was not repeated.

L. P. Gay<sup>23</sup> notes an instance of agonizing lower abdominal pain in a man of 40. Temperature of 102° F and leukocytes to 17,000 were present. The abdomen was rigid, distended, with marked tenderness in both lower quadrants. The pelvic colon was palpable, spastic and very tender. The patient had had a severe gastrointestinal upset from pork two years before and the evening before this attack he had eaten pork sausage. The attack subsided spontaneously but a similar though mild episode followed the eating of cooked pork at a later date.

A more recent paper by Hampton<sup>24</sup> is concerned with Henoch's purpura based on food allergy. It includes one case which has some points in common with the syndrome under discussion. Thus, in addition to abdominal pain some febrile response was noted which disappeared when the suspected foods, eight in number, were finally eliminated from the diet. Skin tests were negative. Two features of this case differ from those here described: diarrhea was a striking symptom and the patient's attacks responded dramatically to hypodermic adrenalin.

Many of the above-cited examples of food allergy have features in common with the syndrome of benign paroxysmal peritonitis and some fairly closely approximate it. However, within the proved allergic group only one case, reported by Cooke,<sup>25</sup> presents the complete clinical syndrome. In this case cure was effected by exclusion of a single food, milk.

*Case 5 (table 2)* A young woman, age 24, suffered with recurring attacks which began when she was two weeks old. In early life the frequency was once a month, the longest period of freedom being 10 weeks. For a year the attacks occurred weekly. In each attack there was a prodromal period of uneasiness, anorexia and abdominal discomfort lasting several hours. Some mild attacks did not go beyond this stage. Next there was a crescendo period with rapid increase of prostration, abdominal colic and generalized pains. Fever, rising as high as 104° F, and leukocytosis as high as 28,800 were then present. No eosinophilia noted. The abdomen was rigid, with tenderness at times as extensive as in general peritonitis, but varying in the location of maximum sensitiveness. There was constant nausea, belching and vomiting. This stage lasted from eight to 16 hours and was followed by a period of rapid recovery. She then felt well and quickly regained the four or five pounds which she had lost in the attack. Exploratory laparotomy was done at the Johns Hopkins Hospital and the appendix removed. It was without effect.

Intradermal tests were entirely negative. The family history for allergy was negative. However, it was decided to exclude those foods most commonly taken from infancy onward. Hence milk, eggs and meat were eliminated from the diet. The attacks stopped. Milk was subsequently added to the diet on two occasions and the well recognized prodromal symptoms appeared at the end of two days. After these two experiences the patient could not again be induced to take milk. When last

seen, after a nine year follow-up the patient had been free of all attacks. She never touched milk and was not then willing to repeat the experiment.

The sudden cessation of attacks of 24 years' duration by the withdrawal of milk and the reproduction of mild attacks on two occasions by the use of milk seem to warrant the diagnosis of an allergy.

Despite the extremely early onset of the disease at two weeks of age the identity of clinical characteristics leaves little room for doubt that this case is an instance of the syndrome here discussed. The abdominal spasm is somewhat unusual, but similar to several of the cases observed by Althausen, Deamer and Kerr. This case proves that paroxysmal peritonitis, with high fever and leukocytosis can be caused by food hypersensitiveness.

Cooke's case possesses additional interest because it was originally published in 1908 by Janeway and Mosenthal<sup>26</sup> as "An Unusual Paroxysmal Syndrome Probably Allied to Recurrent Vomiting." These writers, then in complete ignorance of the cause of their patient's illness, made the following observations which logically apply to the whole syndrome of paroxysmal peritonitis. "It seems most unlikely that any inflammatory focus could continue for so many years to produce exactly similar attacks without leading to more serious consequences or giving other evidences of its existence." The clinical accuracy of this point of view is such that no attempt will be made to discuss obscure organic causes which could not possibly explain this unusual syndrome.

A further observation from the same paper is likewise pertinent to the present problem. "As for the ubiquitous diagnosis for all unexplained crises, hysteria, we think that scarcely warrants serious consideration. Hysterical pain is common, hysterical fever may exist, hysterical leukocytosis seems out of the question." It must be granted that in the light of present concepts of the psychosomatic causation of disease one cannot altogether exclude the possibility of a psychogenic component in this bizarre syndrome.

Certain observations in the author's series likewise provide support for the allergic theory. The clinical course of the disease fits well into the allergic category, for it is paroxysmal, benign, and its onset is in early life. The vascular dilatation and hyperpermeability which seem to comprise the essential lesion of this disease are likewise typical of the allergic response. The high fever alone does not suggest an allergic reaction. However, as has been shown, febrile reactions may be due to food allergy. It may incidentally be noted that other well established forms of allergic reaction such as serum disease are typically febrile.

Four of the five cases in the present series give a positive familial history for allergy. In case 2 this was particularly of the gastrointestinal type. Case 3 is himself clearly an allergic individual. Another possibly significant observation is the occasional interval eosinophilia noted in cases 4 and 5. All these findings add their weight to the thesis that this disease belongs within the allergic category. Rather indirect evidence against this is the



lack of response to hypodermic epinephrine administered in the acute episode (cases 1, 2 and 5)

A more serious argument against the allergic postulate is the difficulty in discovering any causative allergic factor. It would be tempting to conclude from some of the observations already noted that all cases of benign paroxysmal peritonitis are due simply to food allergy. Such an assumption is not warranted by the available experience. In three of the author's series careful investigation has not revealed the causative food allergen. In the remaining two cases less complete study has likewise been negative. The delayed form of food allergy with negative skin tests is a notoriously complex problem. In some instances, despite carefully kept food diaries and stringent adherence to trial diets, the offending foods may escape detection. However, efforts along these lines must be continued as food allergy is at present the only available clue to possible cure of these cases.

It is possible that some other allergic mechanism operates in those cases without evident food hypersensitiveness. Bacterial sensitization, whether to upper respiratory or gastrointestinal flora, is a rather remote possibility. There is no convincing evidence, either from the clinical or laboratory point of view, to support this theory. If such bacterial vascular sensitization were postulated it would be of a different order from that possibly active in acute lupus erythematosus disseminatus<sup>27</sup>. Nor would it be related to the type of vascular allergy which is characterized by marked blood and tissue eosinophilia and often terminates in periarteritis nodosa<sup>28</sup>.

Thus, one may view this disease as allergic in nature but with many of the cases beyond solution by present technics. This would be analogous to what obtains in other presumably allergic disorders such as bronchial asthma or vasomotor rhinitis. Or it may be grouped with other paroxysmal, and often vascular, disturbances such as migraine, Ménière's syndrome, angio-neurotic edema or the Henoch-Schoenlein form of purpura. Some cases of each of these have been shown to be allergic, although the vast majority belong at present to the category of disorders of unknown origin.

Within the past year M. T. Moore<sup>29</sup> has reported a case of paroxysmal abdominal pain of 31 years' duration in which an abnormal electroencephalogram was found, and the attacks prevented by means of dilantin therapy. Nothing was stated as to the presence of fever or unusual abdominal findings. In a personal communication Moore writes "The patient had a mild rise of temperature during the bouts. Insofar as the actual status of the abdomen was concerned, nothing more than increased intestinal activity was apparent." In case 2 of the author's group an entirely normal electroencephalogram is reported by Dr. Hans Strauss. The clinical manifestations of the present series appear to offer distinct differences from Moore's case but further observations along these lines may be worthwhile.

## DIAGNOSIS AND TREATMENT

This syndrome presents a double problem in diagnosis. The first is that of the acute episode when first observed, the second that of the disease in its entirety. The correct diagnosis of the acute paroxysm, particularly when encountered early in the course of the illness, may be extremely difficult. As already noted the attack may closely simulate acute appendicitis and emergency operation be advised (see cases 1 and 5). Acute cholecystitis may also be suspected although the youth of the patient is likely to argue against this diagnosis.

Certain characteristics of the acute attack of benign paroxysmal peritonitis differ from the more usual surgical inflammations of the abdomen. Any of the following findings should place the physician on his guard:

1. An unusual degree of abdominal tenderness, both direct and rebound, beyond what would be expected with a surgical lesion of equivalent duration.

2. A considerable febrile reaction,  $103^{\circ}$  F or more, unusual for a surgical inflammation in an early stage. If the patient is observed for 24 hours the temperature drops strikingly, often to normal.

3. Skin lesions of a vascular type may be present. Even a single urticarial wheal should be given its due clinical weight.

4. Onset with pain in either shoulder or the occurrence of a pleuritic element in the patient's pain, too early to be explained by perforation or subphrenic extension.

5. A personal or family history of allergy.

An additional point of practical importance to correct diagnosis is that neither the presence of leukocytosis and polynucleosis nor the absence of eosinophilia excludes benign paroxysmal peritonitis.

The paroxysms are often just atypical enough so that emergency operation is avoided. The patient suffers through several such episodes, all subsiding spontaneously, and he is regarded less and less as a surgical problem. Diagnostic investigations are then carried out without positive result. The diagnosis becomes increasingly obscure as all the usual causes of abdominal pain and fever are consecutively excluded. Before the disease has been of too long duration acute mesenteric adenitis, abdominal Hodgkin's disease, hepatic abscess and undulant fever will be considered. Persistently negative findings and the further course of the disease finally rule out all such possibilities. In women the condition must be distinguished from the syndrome of ruptured Graafian follicle or corpus luteum cyst of the ovary, with peritoneal irritation. The absence of any evidence of internal bleeding and the frequent recurrence of attacks over many years ultimately excludes these causes also.

Sooner or later it is recognized that the syndrome falls into no accepted category. Psychiatric causes will be considered and even malingering will be thought of. However, the obviously genuine clinical pattern of the disease, together with the fever and leukocytosis, excludes the latter and makes

the former unlikely. If cases occur where the fever is slight or on occasion absent the patient may be permanently classified as "neurotic," often with no further effort made to understand the origins of his illness.

Exploratory laparotomy is likely to be recommended when all other diagnostic measures have failed. As this disease becomes more widely recognized, operation for this purpose will become unnecessary. However, in the individual case where abdominal exploration is deemed wise it is urged that it be done during an acute attack rather than in a free interval. The underlying pathologic reaction of the disease can be observed, or other lesions such as an internal hernia with incomplete obstruction, or torsion of an internal cyst or appendix epiploica, rare though they be, will be discernible only at this stage. An interval operation is likely to be totally unrevealing.

Operation should not be performed until the patient has had the benefit of a complete allergic study. Intradermal testing though of possible value forms the least part of this investigation. Painstaking and prolonged experimentation with trial and addition diets together with the use of a food diary comprise the most valuable methods. The allergic approach, being at present the only fruitful one, should be pushed to the utmost.

From the standpoint of medicinal therapy various pharmacologic agents should be tried. Adrenalin, gynergen, atropine sulfate, ephedrine, and nicotinic acid should all be used during the acute attack in an effort to abort it. Continuous treatment with several of these drugs may also be attempted in the hope that attacks may be prevented. Experience with both forms of therapy has thus far been disappointing.

### SUMMARY

Five cases are presented illustrating an unusual syndrome consisting of paroxysms of intense abdominal pain with fever as high as 105° F. Severe prostration, marked signs of peritoneal irritation, as well as nausea and vomiting, are invariable accompaniments. Urticaria and chest pain of a pleuritic type may occur. Onset of the disease is characteristically in early life and the attacks recur frequently over many years. The patients' general health remains unimpaired. The nature of this bizarre disorder is discussed together with its probable relationship to allergy. Suggestions are offered as to diagnosis and treatment.

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### BIBLIOGRAPHY

- 1 OSLER, SIR WM. On the visceral complications of erythema multiforme, *Am. Jr. Med. Sci.*, 1895, cx, 629.
- 2 OSLER, SIR WM. The visceral lesions of purpura and allied conditions, *Brit. Med. Jr.*, 1914, i, 517.

- 3 CHRISTIAN, H A Visceral disturbances in patients with cutaneous lesions of the erythema group, Jr Am Med Assoc, 1917, lxx, 325
- 4 TRIMBLE, I R Erythematous group of skin diseases with especial reference to abdominal pain, Jr Am Med Assoc 1931, xcvi, 2010
- 5 OSLER, SIR WM Hereditary angioneurotic edema, Am Jr Med Sci, 1888, xci, 362
- 6 BOGART, A H The surgical significance of intestinal angioneurotic edema, Ann Surg, 1915, lxi, 324
- 7 HENoch, E Zusammenhang von Purpura und Intestinalstoeurungen, Berl klin Wchnschr, 1868, v, 517, Über eine eigentümliche Form von Purpura, Ibid, 1874, vi, 641
- 8 POLL, D Erythema crises of the visceral group, Jr Mt Sinai Hosp, 1938, iv, 97
- 9 FRASER, I Purpura simulating the acute abdomen, Lancet, 1930, ii, 525
- 10 ALTHAUSEN, T L, DEAMER, W C, and KERR, W J The false "acute abdomen", Henoch's purpura and abdominal allergy, Ann Surg, 1937, cvj, 242
- 11 ORTON, L A case of poisoning by eggs, Practitioner, 1886, xxxvi, 365
- 12 SCHOFIELD, A T A case of egg poisoning, Lancet, 1908, i, 716
- 13 SMITH, H L Buckwheat poisoning, Arch Int Med, 1909, iii, 350
- 14 DUKE, W W Food allergy as a cause of abdominal pain, Ann Int Med, 1921, xviii, 151
- 15 ROWE, A H Food allergy, its manifestations, diagnosis and treatment, 1931, Lea and Febiger, Philadelphia
- 16 EFRON, B G Gastrointestinal manifestations in allergy, New Orleans Med and Surg Jr, 1932, xxiv, 540
- 17 FRIES, J H, and MERRILL, G A Allergic abdominal pain in children, Am Jr Dis Child, 1936, lxi, 1107
- 18 LAROCHE, G, RICHTER, C, JR, and ST GIRON, F Alimentary anaphylaxis, 1930, Transl, U of Cal Press
- RICHTER, C, JR Food anaphylaxis, Jr Allergy, 1931, ii, 76
- 19 ALEXANDER, H L, and EIERMAN, C H Food allergy in Henoch's purpura, Arch Dermat and Syph, 1927, xvi, 322
- 20 EIERMAN, C H Allergic purpura, South Med Jr, 1935, xviii, 341
- 21 KAHN, I S Henoch's purpura due to food allergy, Jr Lab and Clin Med, 1929, xiv, 835
- 22 CARR, J G Hypersensitiveness to milk complicating the treatment of duodenal ulcer, Med Clin N Am, 1926, i, 1409
- 23 GAY, L P Acute allergic abdomen, Jr Missouri State Med Assoc, 1934, xxxi, 385
- 24 HAMPTON, S F Henoch's purpura based on food allergy (Case 2), Jr Allergy, 1941, xii, 579
- 25 COOKE, R A Gastrointestinal manifestations of allergy, Bull New York Acad Med, 1933, ix, 15
- 26 JANEWAY, T C, and MOSENFELT, H O An unusual paroxysmal syndrome, probably allied to recurrent vomiting, Trans Assoc Am Phys, 1908, xiii, 504
- 27 BAEHR, G Disseminated lupus erythematosus Textbook of Medicine, Ed CICHL, R L Sixth Edition, 1943, W B Saunders Co, p 457
- 28 HARKAVY, J Vascular allergy, Jr Mt Sinai Hosp, 1942, viii, 592
- 29 MOORE, M T Paroxysmal abdominal pain, a form of focal symptomatic epilepsy Jr Am Med Assoc, 1944, cxlii, 561

# TISSUE CALCIFICATION AND RENAL FAILURE PRODUCED BY MASSIVE DOSE VITAMIN D THERAPY OF ARTHRITIS<sup>1</sup>

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MASSIVE doses of vitamin D have been used in the treatment of arthritis during the past decade<sup>1, 2</sup> Symptoms and physical disabilities of some patients have apparently improved on this régime The clinical reports have usually implied that the toxic effects of these large doses are insignificant<sup>3, 4, 5, 6, 7</sup> In this report two cases of renal damage secondary to prolonged therapy with vitamin D are described In one of these extensive calcification of soft tissues was readily demonstrable

## CASE REPORTS

*Case 1 (E S)* This English housewife was first admitted to New Haven Hospital in 1932 at the age of 47 for study of a painful, deforming arthritis of the extremities which had begun 18 years earlier Despite tonsillectomy, two antrotomies, a submucous resection, dental extractions, abdominal laparotomy, foreign protein injections, and vaccine therapy the disease had been progressive from its onset The patient had, however, been well otherwise

At the time of this admission and during five subsequent admissions in the next two years the abnormal physical findings were limited to the extremities The soft tissues of the hands and feet were atrophied, deformity and markedly restricted range of motion of the large and small joints of all extremities, typical of rheumatoid arthritis, were present Partial ankylosis of the hip and shoulder joints was evident The patient also had chronic pansinusitis and deafness of the conduction type

Laboratory studies at this time were entirely within normal limits (table 1a) Roentgenographic examination of the right wrist and hand (figure 1) and of the hips revealed narrowing of the joint spaces with thinning of the adjacent bone There was no generalized osteoporosis

The patient did not improve significantly under physiotherapy, nor following courses of glycine and of dinitrophenol She was not seen again for eight years During this period she received local treatment for the sinusitis The arthritis persisted and markedly restricted the patient's activity From 1936 to 1942 she took 150,000 to 200,000 units of vitamin D daily as therapy of the arthritis Attempts to increase the dosage to 450,000 during a two month period in 1941 produced gastrointestinal distress In May 1942 a swelling appeared near the left wrist and the patient discontinued the intake of vitamin

She returned in November 1942 for the first of a series of four admissions for treatment of localized fluctuant swellings at the left wrist and the right ankle The physical findings except for further loss of hearing, were otherwise unchanged The patient did not have hypertension

Repetition of laboratory studies revealed anemia and renal insufficiency (table 1b) Azotemia, low specific gravity of urine, two plus albuminuria, casts, and a decreased

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TABLE I

	Blood			Serum				Urine			
	Erythrocytes, per cu mm	Hgb gm	NPN, mg per cent	Albumin, gm per cent	Globulin, gm per cent	Ca mg per cent	P mg per cent	Alb	Casts	Spec Grav-ity	PSP Excretion per cent
Patient E S											
A Before vitamin D											
1932	4 6	13	20	4 24	2 85	10 20	3 81	0	0	1 028	
1934	4,8	14	34	3 93	3 26	10 86	3 65	0	0	1 023	
B After 6 years on vitamin D											
November 1942	2 9	8 5	67	3 69	2 06	15 37	4 53	++	+	1 013	15
C After cessation of vitamin D											
April 1943	3 7	10 5	53	4 02	1 98	13 81	4 45	+	+	1 013	30
December 1943	4 2	12 5	46	3 48	2 91	11 77	3 60	+	0	1 013	30
January 1945	4 2	10 5	50	4 26	2 76	9 24	2 45	0	0	1 009	35
Patient H W											
D After 7 months on vitamin D											
October 1944	3 0	9 0	55	4 52	2 41	14 47	5 23	++	+	1 005	20
E After cessation of vitamin D											
November 1944	3 6	9 6	41	4 57	1 71	11 99	3 30	+	+	1 014	27
January 1945	4 1	11 5	47	4 22	2 11	9 40	3 24	+	+	1 015	35

excretion of phenolsulphonphthalein dye were all present. In addition, the concentrations of calcium and phosphorus in serum had become elevated, in contrast to their previously normal values. Roentgenograms showed decalcification of all bones except the skull, narrowing or destruction of joint spaces, and extensive calcific deposits in the soft tissues of the hands, wrists (figure 2), and right ankle. There was no calcification seen in the abdominal organs.

The localized swellings were incised, yielding red gelatinous or white chalk-like material containing calcium. These lesions healed by granulation only after months of persistent discharge.

One and one half years after cessation of vitamin D therapy the concentration of serum calcium had fallen to 11.77 milligrams per cent, and the serum phosphorus was normal. The albuminuria had diminished to one plus. Two and one half years later the swellings had not recurred and the patient's hearing had improved distinctly. The serum calcium and phosphorus values had returned to normal. The non-protein nitrogen of the blood was still elevated at 50 milligrams per cent, but the urine was free of albumin and casts (table 1c).

Repeat roentgenograms at this time revealed a striking decrease or complete disappearance of the calcium deposits in the soft tissues of the hands, wrists (figure 3), and of the right ankle. In addition complete destruction and absorption of some of the bones of the wrists were evident, together with concentric decrease in the head of the right femur and movement of the right acetabular surface upward.

**Case 2 (H W)** This 56 year old Irish widow was admitted initially with intermittent abdominal cramps, nausea, and vomiting of three months' duration associated

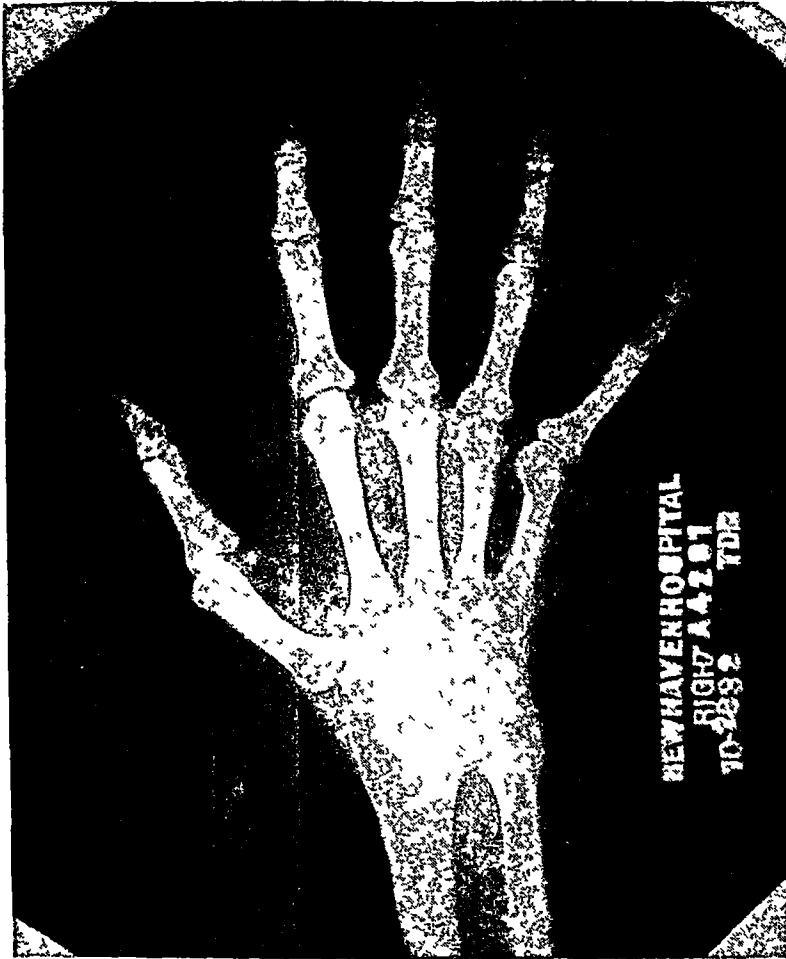


FIG 1 Roentgenogram of patient E S in 1932 showing atrophic arthritis of the right hand and wrist of 18 years' duration



FIG 2 Roentgenograms of hands and wrists of patient E S in 1942 showing destruction of joint spaces, osteoporosis of the adjacent bone, and calcification in the periarticular tissues after six years of therapy with vitamin D

with an 11 pound weight loss. The past history included scarlet fever at the age of two, a stay of 18 months in a sanatorium at the age of 18 for treatment of pulmonary tuberculosis, irradiation therapy of uterine fibromata at the age of 34, and pain in the right hip and leg following a minor fall at the age of 44. During the 10 years preceding admission the patient had experienced intermittent pain in the joints of all extremities without any objective change noted. In January 1944 the patient was advised by her physician to take vitamin D as treatment for the arthritic pain. The initial daily dose of 50,000 units was increased in the course of the next eight weeks to 500,000 units and maintained at that level for five months, ending two months before admission. The patient experienced nausea and vomiting for about 24 hours following each increase in dosage. During this seven month period she took at least one quart of milk daily.



FIG 3 Repeat roentgenograms of patient E S two and one half years after cessation of vitamin D administration showing partial or complete resorption of calcium deposited in the soft tissues. Striking destruction or complete disappearance of the bones of the wrists is evident, most marked on the left.

Review of systems indicated that within the year preceding admission the patient had developed a slight cough, exertional dyspnea, and orthopnea and that the blood pressure had been found to be high.

In the course of this and two subsequent admissions to the hospital the blood pressure ranged from 240 mm Hg systolic and 120 mm diastolic to 190 mm systolic and 100 mm diastolic. Positive findings on physical examination included the presence of resolving hemorrhages in the left fundus, cardiac enlargement, a precordial systolic murmur, edema of the ankles, and Heberden's nodes.

Laboratory studies revealed hypochromic anemia, an elevated blood non-protein nitrogen content, urine of low specific gravity, and poor excretion of phenolsulphonphthalein dye (table 1d). The concentration of serum bicarbonate was slightly reduced. A distinct hypercalcemia existed together with an increased concentration of serum phosphorus. Roentgenographic studies showed fibrotic pulmonary tuberculosis.



of the right upper lobe, cardiac enlargement, diverticulosis of the descending colon, and a compression fracture of the twelfth dorsal vertebra. The skull was osteoporotic, proliferations of bone were seen at the knee and hip joints, and on the vertebral bodies, of the type associated with hypertrophic osteoarthritis. There was no metastatic calcification. The electrocardiogram was characterized by low T-waves in limb Leads I and II, and slight left axis shift. Urine cultures were negative.

With digitalization and rest in bed the patient lost 4.3 kilograms of edema fluid. Repeated serum calcium and phosphorus determinations showed a gradual return to normal values during the next 12 weeks. The hypertension and the renal failure persisted (table 1e) †

## DISCUSSION

These two cases indicate clearly that patients treated for a prolonged period with massive doses of vitamin D may develop calcification of soft tissues and renal damage. Renal complications may be less uncommon than the paucity of such clinical reports would indicate, since the azotemia and minimal albuminuria which characterize them might be overlooked or ascribed to other causes.

Vitamin D in large doses provokes a hypercalcemia, and increases the calcium content of the soft tissues, particularly of the kidney.<sup>8</sup> The hypercalcemia favors metastatic calcification. This may be facilitated by local tissue injury already present, or produced by the vitamin D itself.<sup>9</sup> Renal calcification affords, therefore, a satisfactory explanation of the renal damage observed in these two patients, even though the calcium deposited in the kidneys was too low in concentration to be demonstrated in roentgenograms. Similar cases have been reported by Thatcher,<sup>10,11</sup> and by Tumulty and Howard,<sup>12</sup> following Putschar's description<sup>13</sup> of calcium deposits in the kidneys of an infant who died with hypercalcemia produced by a preparation of irradiated ergosterol.

This impairment of renal function by vitamin D is to a considerable extent reversible. The kidney function in the two young patients reported by Tumulty and Howard improved following cessation of vitamin D therapy, but poor concentrating ability persisted as a residuum of the renal injury produced by irradiated ergosterol.<sup>12</sup> In the two cases reported in the present paper interruption of vitamin D after months and years of therapy was followed by a return of renal function toward normal without complete resolution. It is of interest in this connection to note that the subcutaneous metastatic calcification of patient E. S. was eventually almost completely reabsorbed. Presumably, a similar decrease in calcium occurred in the kidney. The extent of the fibroblastic proliferation about the calcified areas in the kidneys probably determines the completeness with which the renal lesions may resolve. However, intrinsic renal disease independent of that produced by vitamin D injury cannot be excluded as a factor limiting the degree of recovery possible.

† (June, 1945) The blood pressure returned to normal limits in March, 1945.

Patient H W received a proprietary form of vitamin D prepared by the Whittier process of heat vaporization and subsequent electrical activation of ergosterol. This product has been reported less toxic than the vitamin D formed by ultraviolet irradiation or ergosterol<sup>3, 4, 5, 6, 7</sup>. However, even in these reports patients treated with the electrically activated product at times developed hypercalcemia, anorexia, nausea, and vomiting. Polyuria and nocturia were also noted occasionally. These symptoms, which disappeared as the dosage was decreased, are identical with the early phases of intoxication with irradiated ergosterol<sup>12, 14</sup>. It would appear, therefore, that vitamin D prepared by either method may produce the same toxic effects. This is confirmed by the experience with the two patients described in this report.

The extensive destruction of bone evident in the wrists and right hip of patient E S is an anomalous development in the natural course of atrophic arthritis. It suggests that the extensive intake of vitamin D together with a low intake of calcium and phosphorus produced disruption of the histology of the bone of the type reported in rats,<sup>15</sup> with subsequent absorption of the injured bone. During the first five of the six years of therapy this patient did not drink milk nor did she receive supplementary calcium. In the last year she took one or two glasses of milk daily during a period of one month.

No clear principle has been formulated for a rational use of vitamin D in arthritis. Its introduction followed the chance finding that patients receiving this vitamin for allergic conditions experienced a coincident improvement in arthritis<sup>1, 2</sup>. It has been shown experimentally in rats that vitamin D may produce either an increase or a decrease in the bone ash, depending upon the dose<sup>16</sup>. This offers, in theory, a logical approach to therapy through attempts either to correct the osteoporosis, or to remove abnormal proliferations of bone. Clinically, however, improvement in arthritis reported during administration of vitamin D is not correlated with any consistent alteration in the density of the skeleton or of exostoses<sup>3, 4</sup>. In serial roentgenograms the osteoporosis may increase, decrease, or remain unchanged. There is also no evidence that improvement is related to the development of hypercalcemia. It seems clear, therefore, that the favorable effects of vitamin D reported in arthritis are unrelated to the metabolism of calcium and phosphorus. This is not surprising in view of the repeated failure to demonstrate any definite abnormality in the calcium and phosphorus balance of patients with arthritis<sup>17, 18, 19</sup>.

As a practical matter, it is evident that the therapy of arthritis with vitamin D demands careful supervision. The patient should never be permitted to continue treatment on his own initiative. Frequent determinations of the serum calcium with prompt reduction of dosage if hypercalcemia develops are essential. Repeated examinations of the urine and blood pressure must be made if renal complications are to be avoided.

The experience with patient H W stresses the necessity for careful questioning about previous intake of vitamin D. Because of the hyper-

calcemia she was at first suspected of hyperparathyroidism. Only through detailed inquiry was the history of vitamin D therapy obtained. This search should be made in all cases of unexplained hypercalcemia, lest the patient be subjected to an unnecessary exploration for an adenoma of the parathyroid gland.

### SUMMARY

1 Two cases are reported of hypercalcemia and of renal failure produced by massive dose therapy of arthritis with vitamin D.

2 Administration of vitamin D to patients with arthritis in amounts sufficient to produce hypercalcemia is unjustified.

3 Hypervitaminosis D is to be considered in the differential diagnosis of hypercalcemia.

The authors are indebted to Dr Hugh M. Wilson, Professor of Radiology, Yale University School of Medicine, and Radiologist-in-Chief of the New Haven Hospital, for interpretations of the roentgenograms.

### BIBLIOGRAPHY

- 1 RAPPAPORT, B. Z., and REED, C. I. Viosterol of high potency in seasonal hay fever and related conditions, *Jr Am Med Assoc*, 1933, **ci**, 105-109.
- 2 DREYER, I., and REED, C. I. The treatment of arthritis with massive doses of vitamin D, *Arch Phys Therap*, 1935, **xvi**, 537-540.
- 3 FARLEY, R. T., SPIELING, H. F., and KRAINES, S. H. Five year study of arthritis patients. Laboratory and clinical observations, *Indust Med*, 1941, **x**, 341-352.
- 4 SNYDER, R. G., and SQUIRES, W. H. A preliminary report on activated ergosterol. Form of high dosage vitamin D in treatment of chronic arthritis, *New York State Jr Med*, 1940, **xl**, 708-719.
- 5 SNYDER, R. G., SQUIRES, W. H., FORSTER, J. W., TRAEGER, C. H., and WAGNER, L. C. The treatment of two hundred cases of chronic arthritis with electrically activated vaporized sterol, *Indust Med*, 1942, **xi**, 295-316.
- 6 SNYDER, R. G., SQUIRES, W. H., and FORSTER, J. W. A six year study of arthritis therapy, *Indust Med*, 1943, **xii**, 291-297.
- 7 LEVINTHAL, D. H., LOGAN, C. E., KOHN, K. H., and FISHBEIN, W. I. Practical management of arthritis, medical and orthopedic, *Indust. Med*, 1944, **xiii**, 377.
- 8 REED, C. I., DILLMAN, L. M., THACKER, E. A., and KLEIN, R. I. The calcification of tissues by excessive doses of irradiated ergosterol, *Jr Nutr*, 1933, **vi**, 371-381.
- 9 SHFLLING, D. H., and ASHER, D. E. Calcium and phosphorus studies. IV. The relation of calcium and phosphorus of the diet to the toxicity of viosterol, *Bull Johns Hopkins Hosp*, 1932, **i**, 318-343.
- 10 THATCHER, L. Hypervitaminosis D, with report of a fatal case in a child, *Edinburgh Med Jr*, 1931, **xxxviii**, 457-467.
- 11 THATCHER, L. Hypervitaminosis D, *Lancet*, 1936, **i**, 20-22.
- 12 TULLITY, P. A., and HOWARD, J. E. Irradiated ergosterol poisoning, *Jr Am Med Assoc*, 1942, **cxix**, 233-236.
- 13 PUTSCHAR, W. Über Vigantolschädigung der Niere bei einem Kinde, *Ztschr f Kinderheilk*, 1929-1930, **xviii**, 269-281.
- 14 HESS, A. F., and LEWIS, J. M. Clinical experience with irradiated ergosterol, *Jr Am Med Assoc*, 1928, **xc**, 783-788.

- 15 SHELLING, D Calcium and phosphorus studies III The source of excess serum calcium in viosterol hypercalcemia, *Jr Biol Chem*, 1932, xcvi, 229-243
- 16 BROWN, H B, and SHOHL, A T XI The alteration of calcium and phosphorus metabolism of normal and ricketic rats produced by irradiated ergosterol, *Jr Biol Chem*, 1930, lxxxi, 245-262
- 17 ROPES, M, SHORT, C L, ROSSMEISL, E, and BAUER, W Calcium and phosphorus metabolism studies in rheumatoid and degenerative arthritis, *Jr Clin Invest (Proc)*, 1937, xvi, 675
- 18 REED, C I, STRUCK, H C, and STECK, T Vitamin D Chemistry, physiology, pharmacology, experimental and clinical investigation, 1939, University of Chicago Press, Chicago, 262
- 19 ROBBINS, C L The effect of dinitrophenol on calcium and phosphorus metabolism, *Jr Nutr*, 1935, v, 187-191

# THE SYNDROME OF PSOAS MYOSITIS AND FIBROSITIS; ITS MANIFESTATIONS AND ITS SIGNIFICANCE IN THE DIFFERENTIAL DIAGNOSIS OF LOWER ABDOMINAL PAIN\*

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PAIN and tenderness in the psoas muscle which is probably attributable to myositis or fibrositis has been known for many years, but its importance in the differential diagnosis of lower abdominal disease has not been emphasized sufficiently. During the past few years I have observed this syndrome in over 50 cases varying in age from 16 to 60 years. It has been mistaken for other diseases in most instances. In 25 of the 50 cases abdominal operations have been performed alone or in conjunction with perineal repair because of mistaken diagnosis. In addition, many of these patients have become extremely anxious regarding their condition because they have consulted several physicians without a diagnosis being established. In some instances the diagnosis of psychoneurosis has been erroneously attached to the patient. It is for these reasons that I wish to call attention to this syndrome, to emphasize its frequency and importance in the differential diagnosis of lower abdominal pain, and discuss its manifestations.

The more common subjective manifestation of this syndrome is pain in the lower quadrants of the abdomen. It may be unilateral or bilateral and is usually dull and aching in character. It may persist for days, weeks, months or even years, but acute exacerbations of sharp pain occur. With careful inquiry it will be noted that the pain is increased with activity which increases the use of these muscles and it is ameliorated by cessation of such activity, although it usually does not entirely disappear. The onset is insidious but may be sudden. Exacerbations and remissions with complete disappearance of symptoms are common, but in some instances it has persisted for years. Sacroiliac syndrome and fibrositis of other muscles are common accompaniments.

The only definite objective manifestation is tenderness over the psoas muscle. This tenderness is increased when the muscle is contracted or stretched and, as a rule, extends from the origin of the muscle along its entire course to the tendon and to its insertion into the femur. Both psoas muscles are frequently involved, but one side is usually the more severe.

The etiology cannot be ascertained in many instances. On the other hand, trauma, defects in body posture, or acute infections appear to be exciting causes. In others the syndrome follows pregnancy or is associated with the sacroiliac syndrome.

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Other conditions usually accompany the psoas fibrositis. The more common of these are sacroiliac syndrome, fibrositis of other muscles, or anxiety manifestations. Only 10 of the 50 cases exhibited manifestations of psoas fibrositis alone. Cases 1, 2 and 3 are typical illustrations of this variety. In cases 1 and 2 the pain was unilateral, whereas in case 3 it was bilateral. Trauma was apparently the etiology in case 1, but no causative factor was ascertained in the other two cases.

Those associated with sacroiliac syndrome may develop following a sacroiliac strain, following pregnancy or from no apparent cause. In such instances the relative prominence of the subjective manifestations of the two syndromes varies. In some the sacroiliac predominates, in others the psoas fibrositis, and in others both are of equal intensity as illustrated by cases 4 and 5.

If fibrositis of other muscles is present the predominating manifestations may be those arising from the psoas muscle or those arising from other muscles. The muscles of the thoracic wall, shoulder and cervical region are the more common ones involved in association with the psoas syndrome. In most instances the pains in the lower abdomen and those in the other muscles are considered by the patient to be separate and distinct diseases. Case 6 is a typical illustration.

The manifestations of anxiety may dominate the picture if the psoas syndrome occurs in a "high-strung" individual, if it is of long standing, if the diagnosis has not been established, or if an erroneous diagnosis has been made. This is typically illustrated by case 7.

In some instances attacks recur for years and various therapeutic measures have been employed without benefit. The patient may have been subjected to unnecessary major surgical procedures as was the situation in case 8.

In the differential diagnosis lesions of the appendix, small bowel, colon, urinary tract, uterus, Fallopian tubes, ovaries and vertebral column must be excluded. Disease of any of these may irritate the psoas muscle and produce the manifestations of fibrositis of this muscle. Appendicitis is extremely difficult to exclude in many instances, but irritation from this cause is usually localized to the body of the muscle and does not extend along the entire course of the muscle and tendon to its insertion into the femur as is usually the case with fibrositis. Involvement of the other psoas major muscle is additional evidence in favor of fibrositis and is against localized irritation due to disease of a neighboring organ. The absence of fever and leukocytosis is against, but does not exclude appendicitis. Diseases of the urinary tract, ovaries, Fallopian tubes, uterus and vertebrae are not likely to be confused with the psoas syndrome if all are considered and an adequate examination is made. The diagnosis of irritability of the colon has been made in many of the observed cases. The tenderness in the cecal and sigmoid regions is suggestive of disease of the colon, but if the sigmoid is moved

to one side one can easily ascertain that the tenderness is in the muscle. The colon may be irritable in some instances, but in most cases of psoas fibrositis it is not.

The treatment employed in most cases has been rest of the affected muscles and salicylates in 5 to 15 grain doses three to four times daily. The response to therapy has been excellent in most instances. In cases with an associated sacroiliac syndrome the additional therapeutic measure of application of adhesive tape to the lower back or a sacroiliac belt may be necessary. Postural defects must be corrected if present and activities involving use of the psoas muscles should be omitted. The anxiety manifestations, if present, are easily controlled and eliminated, as a rule, when the condition is explained to the patient and when the response to the treatment is demonstrated. The psoas fibrositis has failed to respond to the above treatment in only two cases. In one the muscle was injected with novocaine without benefit, but later responded to the administration of neocincophen. The other patient, case 6, became convinced that the pains were arising in the muscles and preferred not to have the muscle injected with novocaine or to take neocincophen. The accompanying fibrositis in her trapezius muscle, however, responded to the injection of novocaine.

#### CASE REPORTS

*Case 1*—A white girl, aged 17 years, first entered the hospital in December 1933 for pain in the right lower quadrant of the abdomen of approximately one month's duration. She had fallen across a frozen corn-row striking the right lower abdomen and the resulting pain was fairly severe but did not incapacitate her. The following morning the pain had disappeared but soreness persisted. Approximately three weeks later she had forgotten about the fall and consulted her local physician who thought that she had appendicitis. After she spent a few days in bed the pain decreased but did not disappear. She was admitted to the hospital and an appendectomy was performed without relief of the pain. A diagnosis of irritability of the colon was made and she was treated for several months without improvement. She returned to the hospital several times during the next three years and was examined by members of the staff of the medical, surgical, gynecological, urological, orthopedic, neurologic, and psychiatric departments without any causative factor being discovered or effective treatment instituted. I had seen the patient upon several occasions before the possibility of psoas fibrositis was considered. The right psoas muscle was extremely tender and when the muscle was contracted or stretched pressure over the muscle was unbearable. There was no evidence of fibrositis elsewhere and the left psoas muscle was not tender. The pain was controlled by salicylate therapy.

*Case 2*—A white male, aged 35 years, consulted me on July 20, 1937, for pain in the left lower abdomen of six weeks' duration. He had been well until the previous June when he had an attack of diarrhea of three days' duration. There was no accompanying fever, chills or melena. A few days later he noted a pain in the left lower abdomen and consulted his local physician. Stool examinations for occult and gross blood and roentgenograms of the colon were negative. The usual regimen for irritability of the colon was followed very rigidly for six weeks without relief. The only abnormal physical finding was tenderness in the lower left abdomen. Proctoscopic examination, repeated examinations of stools for blood and pathogenic organisms and roentgenograms of the colon were negative. Several modifications of the

above regimen were tried for four months without relief. Finally the possibility of psoas fibrositis was considered and the left psoas muscle was only slightly tender until it was contracted or stretched and then it became extreme. The pain disappeared following salicylate therapy.

*Case 3* A white single woman, aged 52 years, consulted me November 12, 1941 for pain in both lower quadrants of the abdomen of four to six months' duration. She had had an appendectomy many years before, but otherwise had been well. She was unable to state the exact time of onset of the pain, but the pain in the right side was the more severe. It was described as dull, aching in character, varied in intensity from barely perceptible to very annoying. She worked in a small postoffice and the handling of packages caused her to stoop and squat a great deal. The pain was almost invariably improved on the days she did not work. Her local physician prescribed the usual regimen for irritability of the colon which gave her no improvement. The only objective manifestation was tenderness over both psoas muscles which was greatly increased by contracting or stretching the muscles. The pain disappeared with salicylate therapy.

*Case 4* A white married woman, aged 26 years, consulted me September 10 1941, for pains in both lower quadrants of the abdomen and in the lower back of three months' duration. She had consulted three physicians and was informed by one that she had disease of her pelvic organs, by another that she had appendicitis, and by the third that she had irritability of the colon. The only objective manifestations were tenderness over both psoas muscles and both sacroiliac regions. The pains were relieved by application of adhesive tape to lower back and salicylate therapy.

*Case 5* A white married woman, aged 24 years, consulted me April 16, 1942, for pain in both lower quadrants of the abdomen of two years' duration. She had had two normal full-term pregnancies and had noticed the pain very soon after the last one. The pain was variable, but had annoyed her most of the time for the two years. A perineal repair and a suspension of the uterus had been performed without relief. The appendix was removed also without amelioration of the pain. The only objective manifestations were tenderness over the psoas muscles and sacroiliac regions. The pain disappeared with salicylate therapy.

*Case 6* A white married woman, nurse, aged 35 years, consulted me February 2 1942 for pain in right lower abdomen of four years' duration and pains in the breasts of two years' duration. She had been examined thoroughly by several excellent physicians and in two widely known clinics without a definite diagnosis being established. She had become greatly concerned and had become convinced that she had some serious disease in the abdomen and in the breasts. These pains increased and decreased, but never completely subsided. Similar pains had been noted in the shoulders, neck and arms, but they would entirely disappear. The physical examination showed that the intercostal muscles, trapezius and psoas muscles were tender and pressure over the psoas muscles reproduced the pain in the lower abdomen. The pains were ameliorated but did not disappear with salicylate therapy. The pain in the left trapezius disappeared following novocaine injection.

*Case 7* A white widowed woman, aged 52 years, consulted me April 7 1942, for nocturnal sweating, palpitation of the heart, loss of weight, hot flashes, nervousness and pains in the lower abdomen. She had enjoyed good health until three years previously. At this time she frequently assisted the nurse in lifting and turning her husband during his final illness and began to note pains in the lower abdomen. These pains subsided after her husband's death but reappeared at intervals. She consulted several physicians and had her appendix removed without benefit. She had been advised to have a hysterectomy, and had followed a regimen for irritability of the colon for over a year without relief. These pains caused her great anxiety and she feared that she had a cancer or tumor. As the anxiety increased these symptoms be-



came the predominant ones. During the previous three months the pains were greatly increased by walking and were ameliorated by resting. She was unable to walk over three city blocks without the pains becoming very annoying. The only objective manifestations were emaciation and tenderness over the psoas muscles which reproduced the lower abdominal pain. The abdominal pains were relieved by salicylate therapy.

*Case 8* A white married woman, aged 65 years, entered the hospital complaining of pain in the right mid and lower abdomen of several months' duration. The attacks of pain began about 15 to 18 years previously, lasted several months each time, and recurred at two to four year intervals. During her initial attack the appendix was removed and during a subsequent attack the uterus and ovaries were removed. These organs showed no definite disease and she obtained no relief from the operations. Later, some abnormality of the right kidney was discovered and the right kidney was removed without relief of the pain. During the last attack a stone was found in the gall-bladder and a cholecystectomy was performed without influencing the pain. The pain apparently subsided spontaneously during each previous attack. It was greatly aggravated in each attack by standing or walking for only a few minutes. The right psoas muscle was very tender and pressure over it reproduced the pain. No other abnormality could be ascertained. This pain subsided with salicylate therapy.

#### SUMMARY

The manifestations of the syndrome of myositis and fibrositis of the psoas muscles are presented. The frequency and importance of this syndrome in the differential diagnosis of lower abdominal pain are emphasized. The reports of eight cases are included to illustrate the variations the syndrome may assume. The therapeutic measures employed and the results obtained are discussed.

# AIDS IN PHYSICAL DIAGNOSIS: SIGNS OVER THE LOWER LEFT LUNG CAUSED CHIEFLY BY CARDIAC ENLARGEMENT\*

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IN 1896 William Ewart, physician to St George's Hospital in London, described<sup>1</sup> what he termed his crucial signs of pericardial effusion. Clinicians have long appreciated Ewart's signs<sup>†</sup> and in 1918 Dr H A Christian<sup>2</sup> reported their presence in 73 per cent of his cases of acute fibrinous pericarditis. L A Connor in the first issue of the American Heart Journal likewise called attention to these signs<sup>3</sup>. We have observed a somewhat similar group of physical signs over the left lower lung but in no case was there evidence of pericarditis or pericardial effusion to explain the physical changes. Likewise we have observed physicians in diagnostic error because of a misinterpretation of these signs.

It is our purpose to call attention to these signs that have not been described adequately in the medical literature and clearly to distinguish them from those of Ewart. It seems that all types of cardiac enlargement may cause these several signs over the left lower lobe and that they are not peculiar to any particular heart shape. In our illustrative cases it will be noted that these signs were associated with general enlargement of the heart, the enlargement of the left ventricle seen especially in hypertensive disease, the enlargement of the auricles and ventricles seen in severe rheumatic heart disease with several valves involved, the enlargement of the heart chiefly in the region of the left auricle from mitral stenosis alone, and finally the rather slight enlargement of congenital type.

We believe our signs represent a compression of the left lower lobe most often caused by an enlarged heart, certainly this is a clinical syndrome that has been appreciated for years but one which curiously has escaped description in recent texts and so has been a neglected fact in recent teaching. However, as Dr John Homans, in delivering the dedicatory address at the Yale Medical Library, said "Discoveries are perennially being made, affirmed, forgotten, lost, found again and finally placed on record and universally accepted."

Vaquez<sup>4</sup> referred to the use of dorsal percussion in measuring heart size and properly accredited Piorry<sup>5</sup> with having introduced this technic in 1866. In this era before the clinical use of the roentgen-ray Barie<sup>6</sup> reviewed the previous work of Pirogoff, Luschka and Poirier who demonstrated on cadavers that the normal left auricle lies just to the left of the sixth to

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† We can find no authority of Ewart's sign accredited with the same in Dorland's dictionary.

seventh dorsal vertebrae and that with a forceful percussion note one might elicit a 3 by 7 cm oval area of dullness in this area that outlined the left auricle. This rather precise and difficult technic was probably accepted by very few clinicians and we wish to add that nothing was said about the other important signs of tactile and vocal fremitus and the auscultatory changes. White<sup>7</sup> also mentions very infrequent changes at the left base occurring especially in rheumatic disease with a large left auricle but nowhere can we discover that this subject has been reevaluated since the clinical application of the roentgen-ray.

The chief sign that we have observed in this topographical area of the left lower lobe has been an area of *dullness* just below the angle of the left scapula. However, this finding is not constant in cardiac hypertrophy nor

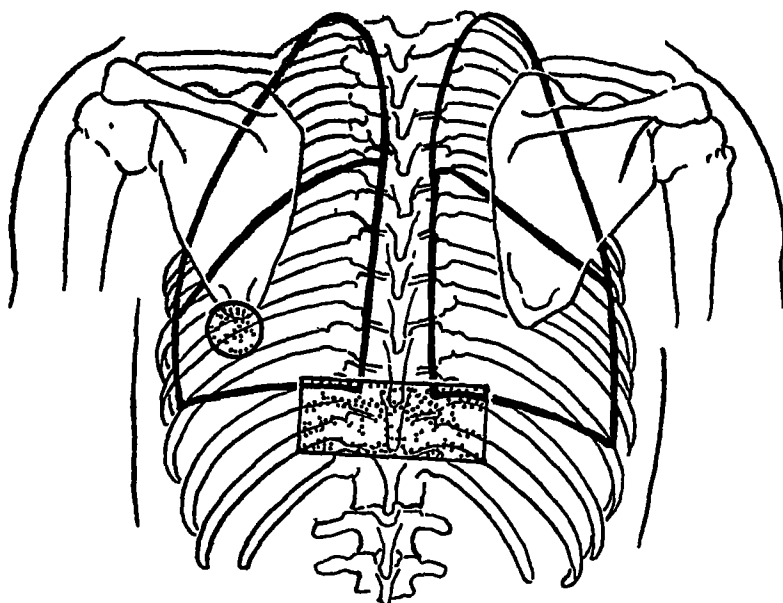


FIG 1 Ewart's signs of pericardial effusion

has it always been present when other abnormal signs were discovered. In some instances the dull note could be elicited only by a very heavy percussion which suggested that the shorter and higher pitched note was due to the sound waves penetrating normal lung and being absorbed or reflected by the enlarged cardiac mass. This concept we have mentioned in a previous publication.<sup>8</sup> The changes in *tactile fremitus* at the left base are difficult to evaluate as in the normal there is greater fremitus over the right base due to the direct anatomical position of the right descending bronchus. *Auscultatory changes* have most often been a prolonged expiration, varying from those described as bronchovesicular to bronchial, in some the breath sounds were diminished, and moist, crepitant râles were heard. The voice sounds in some were altered so as to give an increased, almost nasal sound. With this group of changes from the normal it is plain that we are not de-

scribing a fixed set of signs but rather indicating that variable changes from the normal occur with surprising frequency over the left base. In fact, we are reminded of Richard Cabot's remark that the pulmonic area is the region of "auscultatory romance" for cardiac murmurs, and we are tempted to add that the region of the left base is the region of "romance" for pulmonary findings.

The explanation for these changes encountered over the left lower lobe has not always been clear, but with anatomic and physiologic facts in correlation we have sought an adequate explanation. Normal variations in size, position and degree of patency of the left lower lobe bronchus may greatly affect physical signs over this lobe, the evidence of Klopstock<sup>9</sup> that the pulmonary blood flow is greatest throughout the left lower lobe also suggests

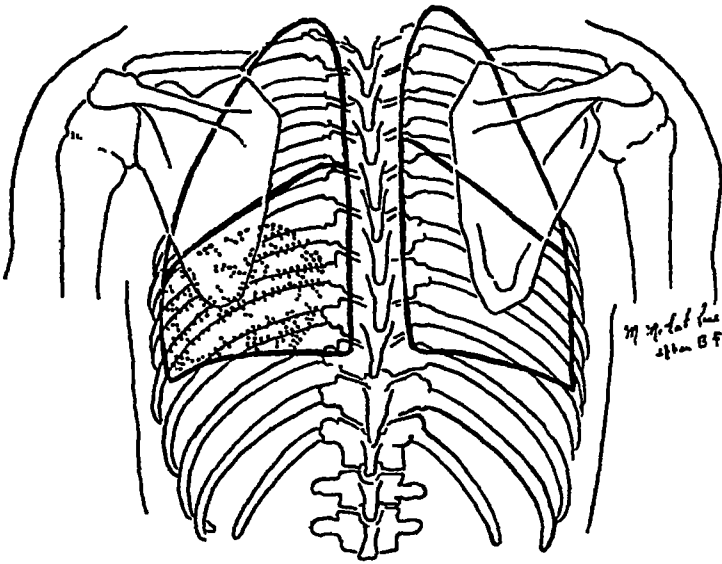


FIG 2 Our signs over left lobe

physical changes in this area, from his observations he postulated that pulmonary emboli (bacterial or coagulated blood) usually strike this lobe first and the clinical evidence of Allen, Linton and Donaldson<sup>10</sup> indicates that 70 per cent of pulmonary emboli slither into the left lower lobe. In addition to these facts it is known from the surgical experience of Churchill<sup>11</sup> that the incidence of bronchiectasis is greatest in the left lower lobe, this point is also stressed in that excellent study of Olgiue's on "The Natural History of Bronchiectasis"<sup>12</sup>

In these patients in whom we have observed changes at the left base we believe we have established the fact that they did not have pulmonary infarction, bronchiectasis, collapse of the lung, pneumonitis, congestion, pleural effusion, an elevated diaphragm or a tumor mass that caused these signs. The ordinary chest films in all cases were scrutinized carefully with these diagnoses in mind and in most cases it will be noted that oblique and lateral films

of the left lung were also obtained. Certainly none of them had pericardial effusion. And in conclusion we believe that in those patients with a markedly enlarged heart, especially those with rheumatic disease in whom the left auricle was enlarged, the abnormal physical signs at the left base are a result of this mass plus the factor of pulmonary compression.

In confirmation we wish to submit these case examples from patients observed in the Massachusetts General Hospital.

Key	{	P = Percussion
		TF = Tactile fremitus
		SV = Spoken voice sounds
		WV = Whispered voice sounds
		BS = Breath sounds

1 *Unit No 314382* A 50 year old housewife with essential hypertension ranging from 210 mm Hg systolic and 120 mm diastolic to 236 mm systolic and 136 mm diastolic was examined on August 7, 1941 and showed P normal, TF normal, SV normal, BS bronchial, 0 râles.

Chest roentgen-rays on August 14, 1941 reported the heart enlarged in the region of the left ventricle, measurements 12.8 cm at apex, 22.1 cm transverse chest. Views in the oblique and lateral view showed no lung disease.

2 *Unit No 318256* A 43 year old male with gout, chronic Bright's disease and hypertension, 215 mm Hg systolic and 145 mm diastolic, on September 25, 1941 physical examination of the chest showed P normal, TF increased, SV increased, BS bronchial.

Chest roentgen-rays that day confirmed the cardiac enlargement, especially to the left, measurements 17.8 cm at apex, 32 cm transverse chest. Left lung clear in oblique and lateral films.

3 *Unit No 117395* A 38 year old man with nephrolithiasis and pyelonephritis, the left kidney had been removed. His blood pressure averaged 134 mm Hg systolic and 86 mm diastolic. On physical examination on July 31, 1941 the chest showed P slight dullness, TF increased, SV normal, BS normal, 0 râles.

Chest roentgen-rays on July 11, 1941. The lung fields were clear, diaphragm normal in position and the heart was only slightly enlarged in the region of the left ventricle. The aorta was tortuous, measurements 14 cm at apex, 28.9 cm transverse chest.

4 *Unit No 74656* A 50 year old housewife with hypertensive heart disease and thyrotoxicosis from a large goiter partially substernal. Blood pressure was 170 mm Hg systolic and 90 mm diastolic. Physical examination of the chest on August 21, 1941 showed P dullness, TF diminished, BS prolonged expiration, fine râles, heart sounds heard.

On June 26, 1941 chest roentgen-rays showed a substernal thyroid with trachea slightly to the left and the heart enlarged in the region of the left ventricle, measurements 12.7 cm at apex, 24 cm transverse chest. The lungs were clear. The substernal goiter was removed on August 9, 1941 and the patient made an uneventful recovery. When examined again on September 17, 1941 the signs at the left base were unchanged.

5 *Unit No 136069* A 50 year old Swedish-American laborer with arteriosclerotic and hypertensive heart disease who entered the hospital in congestive heart failure. After loss of edema and the signs of active failure the physical examination showed on March 4, 1944, P dullness, TF dim, BS slightly prolonged expiration, 0 râles.

Roentgen-rays of chest on March 9, 1944 showed the left lung clear in the anteroposterior and oblique views. The heart was generally enlarged, especially in the region of the left ventricle. The heart measured 18 cm at the apex and transthoracic measure was 31 cm.

6 *Unit No 312553* A colored boy of 19 entered the hospital with active rheumatic fever and rheumatic carditis. The blood pressure was 120 mm Hg systolic and 80 mm diastolic. On physical examination it was thought that the heart was normal in size and yet the chest on August 7, 1941 showed P slight dullness, TF increased, WV increased, SV nasal, BS normal.

Chest roentgen-rays on July 29, 1941 showed heart enlarged to the right consistent with a congenital heart lesion. The left auricle and pulmonary artery were prominent, measurements 14.4 cm apex, 28 cm transverse chest. The lung fields were clear, even in the oblique view.

7 *Unit No 312150* A 64 year old woman thought to have both hypertensive and rheumatic heart disease with only a single valve involved, mitral stenosis. Blood pressure 214 mm Hg systolic and 90 mm diastolic. Examination on July 27, 1941 showed P slight dullness, TF normal, SV normal, BS increased expiration, 0 râles.

The chest roentgen-ray revealed only slight rounding of the left ventricle, and the left lung even in lateral view was clear.

8 *Unit No 343523* A 23 year old boy with rheumatic heart disease, mitral stenosis and regurgitation, in congestive failure. Blood pressure 160 mm Hg systolic and 60 mm diastolic. Examination on March 5, 1942 showed P woody note, TF increased, VS increased, BS prolonged expiration, 0 râles.

The roentgen-rays of the chest anteroposterior and lateral on March 10, 1942 showed the heart enlarged both to the right and left in the region of the auricles and ventricles. Measurements were 25 cm apex and 29.2 cm transverse chest.

9 *Unit No 306797* A 44 year old housewife with rheumatoid arthritis and rheumatic heart disease with mitral stenosis. She entered the hospital with painful, swollen joints but no cardiac symptoms. Blood pressure was 100 mm Hg systolic and 70 mm diastolic. Examination on August 2, 1941 showed expansion equal, P dullness, TF increased, SV increased, BS prolonged expiration, few râles.

The roentgen-rays of the chest on June 20, 1941 presented the appearance of an enlarged left auricle typical of mitral stenosis. Measurements were 11.9 cm apex, 23.1 cm transverse chest. The oblique view showed no disease of the left lower lobe.

10 *Unit No 128523* A 15 year old boy entered the hospital with severe rheumatic heart disease with mitral stenosis and aortic stenosis and regurgitation. The blood pressure was 125 mm Hg systolic and 56 mm diastolic. Examination on August 27, 1941 showed P normal, TF increased, BS prolonged expiration, 0 râles.

The chest roentgen-rays on August 26, 1941 showed a heart markedly enlarged to both sides with involvement of both ventricles and especially the left auricle. Measurements 17.5 cm at apex, 24.7 cm transverse chest. Oblique showed the left lower lung clear. This case is surprising in that the changes were not as distinct as the heart size would lead one to suspect.

11 *Unit No 289436* This 26 year old Italian man had rheumatic fever recurrent, and a long-standing rheumatic heart with aortic regurgitation and probably mitral stenosis. Blood pressure 140 mm Hg systolic and 40 mm diastolic. On July 24, 1941 the chest examination disclosed P dullness, TF normal, SV nasal, BS diminished, 0 râles.

The roentgen-ray of the chest on August 9, 1941 showed an enlarged heart with enlargement in the region of the left auricle and right ventricle, measurements were 13.8 cm at apex, 30 cm transverse chest. The left lung appeared clear in the lateral and oblique views also.

12 *Unit No 14837* A 28 year old Irishman with severe rheumatic heart disease

with mitral stenosis and regurgitation, aortic stenosis and regurgitation and tricuspid regurgitation. Blood pressure 108 mm Hg systolic and 74 mm diastolic. P slight dullness, TF normal, SV-increased, WV increased, BS bronchial, 0 râles.

Roentgen-rays of the chest on July 25, 1941 showed the heart enlarged in the region of the left auricle, and on fluoroscopy calcification of the mitral valve was seen. There was also slight enlargement of the pulmonary conus and the right side of the heart. Measurements at apex 12 cm, transverse chest 28 cm. The lateral views showed no disease in the left lower lung.

#### BIBLIOGRAPHY

- 1 EWART, WILLIAM. Practical aids in the diagnosis of pericardial effusion, in connection with the question as to surgical treatment, *Brit Med Jr*, 1896, 1, 717.
- 2 CHRISTIAN, H. A. The frequency of pulmonary compression signs in acute fibrinous pericarditis, *Jr Am Med Assoc*, 1918, lxxi, 419.
- 3 CONNOR, LEWIS A. On the diagnosis of pericardial effusion with special reference to the physical signs over the posterior aspect of the thorax, *Am Heart Jr*, 1925-26, 1, 421.
- 4 VAQUEZ, HENRI, and LAIDLAW, G. Diseases of the heart, 1925, W. B. Saunders, Philadelphia, p. 58.
- 5 PIORRY, P. A. Traite de plessimetrie et d'organographie, 1866, A. Delahaye, Paris.
- 6 BARIE, ERNEST. L'exploration de l'oreillette gauche (Examen du coeur, par les region dorsale), *Bull med Paris*, 1897, 11, 701.
- 7 WHITE, PAUL D. Heart disease, 1931, Macmillan Company, New York, p. 53.
- 8 CHAPMAN, E. M., and GOLDSTEIN, A. The physics of sound with particular relation to examination of the patient, *Jr Lab and Clin Med*, 1943, xxviii, 1535.
- 9 KLOPSTOCK, ROBERT. *Klin Wchnschr*, 1933, 11, 1602.
- 10 ALLEN, A. W., LINTON, R. R., and DONALDSON, G. A. Thrombosis and embolism, *Ann Surg*, 1943, cxviii, 728.
- 11 CHURCHILL, E. D., and BELSEY, R. Segmental pneumonectomy in bronchiectasis, *Ann Surg*, 1939, cix, 481.
- 12 OIGIVIE, ALAN G. The natural history of bronchiectasis, *Arch Int Med*, 1941, lxxviii, 395.

# DIAGNOSIS AND SURGICAL TREATMENT OF MENIERE'S DISEASE (HYDROPS OF LABYRINTH) \*

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IN 1861 Ménière first described the syndrome which bears his name. It is characterized by recurring attacks of vertigo accompanied by tinnitus, deafness and, sometimes, nausea and vomiting. Another term is "Meniere's symptom complex."

There are a number of conditions in which the Meniere syndrome may be present, as for example, catarrhal or suppurative middle ear disturbances, allergy, hemorrhage or thrombosis of labyrinthine vessels, toxic neuro-labyrinthitis, multiple sclerosis, neurosyphilis, arteriosclerosis of the cerebral vessels and neoplasms. However, there remains a large group of cases exhibiting the syndrome that show no evidence of vascular, inflammatory or neoplastic processes involving the labyrinth, eighth nerve or its connections with the brain stem, the so-called idiopathic group. In recent years the term "Ménière's disease" has been used frequently to designate this group but, unfortunately, it has been very loosely applied both in this country and in England. This has resulted in many cases that exhibit the syndrome being erroneously diagnosed as Ménière's disease simply because they were insufficiently studied and the cause of their symptoms not determined. In 1938, Hallpike and Cairns<sup>2</sup> were the first to report on pathological changes in the labyrinth in two cases characteristic of this idiopathic group. Since then the temporal bones of some 15 further cases have been examined histologically, confirming their findings and apparently establishing a definite pathological entity. The labyrinth on the affected side showed a hydroph or distention of the endolymphatic system in all cases. Although the pathological process itself is now recognized, the etiology and nature of it are still unsolved. It had been suspected for years that the cause of many of these recurring labyrinthine attacks was an increased intralabyrinthine pressure or glaucoma of the labyrinth. Whether this be due to increased secretion of endolymph, a decreased resorption or a chemical imbalance has yet to be proved, but there is evidence supporting each of the three theories. Knowing the pathological process it is now possible clinically to differentiate these cases from all others showing the symptoms of vertigo, deafness and tinnitus and we believe the term "Ménière's disease" should be applied to this pathological condition and this alone.

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Before describing the symptomatology it might be well to define the term "vertigo." Patients' conceptions of vertigo or dizziness vary tremendously. It is a subjective symptom and we must rely on the patient's ability to describe his feeling. What the patient may call dizziness may prove to be a faintness, giddiness, light-headedness, blurring of vision, or a strange feeling in the head. True vertigo is always characterized by a sense of motion, whether linear or rotary, and a disorientation in space. It is objective when a patient's surroundings seem to move and subjective when the patient seems to move in relation to his surroundings. There is always an uncertainty of balance. The symptoms may be relatively mild and the patient staggers as though he were drunk or they may be more severe and the individual will actually fall. Secondary symptoms of nausea and vomiting, when present, are indicative of the acuity and severity of the vertigo.

The cardinal symptoms of Ménière's disease or hydrops of the labyrinth are paroxysmal attacks of vertigo associated with deafness and tinnitus, of varying intensity and frequency, often accompanied by nausea and vomiting. General physical examination and local otoscopic examination may be entirely negative. In the early stages of this disease, it is not uncommon for the vestibular labyrinth or cochlea to be involved separately, so that an accurate diagnosis cannot be made. However, with succeeding attacks, both parts of the labyrinth become jointly involved and a true diagnosis can be readily reached.

1 The deafness usually varies in severity from time to time and involves the entire scale. There are decreased bone conduction, diplacusis and distortion of sound. The patient hears tones at different pitches in the two ears. If the condition continues over a period of years, the deafness often becomes more profound and no longer shows much variation in degree. The diplacusis and distortion are then no longer noticeable because of the severity of the deafness. Hearing tests are suggestive of a uniform nerve deafness in the affected ear.

2 Tinnitus nearly always accompanies the deafness, and this symptom is usually of a double nature, a high pitched ringing or hissing which is not bothersome and a low pitched pounding or roaring, often synchronized with the heart beat, which is most troublesome and, in some cases, is complained of as bitterly as the vertigo.

3 Labyrinthine activity. Caloric tests show either a non-functioning or hypoactive labyrinth on the affected side and the reaction to caloric tests frequently varies at different times. As a general rule, the more severe the deafness, the less the response of the labyrinth to the caloric test. The unaffected labyrinth will also usually show a diminished response to caloric stimulation. This is especially true of the vertical canals and would appear to be a physiological attempt on the part of Nature to balance or equalize the activity of the opposing labyrinths. These symptoms and signs are suggestive of a varying endolymphatic distention with an accompanying variation in

the sensitivity of the end organs involved. This accounts for the diplacusis, distortion of hearing, varying severity of deafness and tinnitus and the diminished response to stimulation of the labyrinth.

Hydrops of the labyrinth is a disease usually occurring in middle and later life. It seems to be more common in males than in females. There are frequently spontaneous remissions, wherein the individual may be free of attacks for months or even years, only to have them recur with increased severity. This condition is usually unilateral and affects only one labyrinth but, in approximately 10 per cent of the cases, the second labyrinth may become involved. Acute attacks may be brought on in one of two opposite ways. First, an increased pressure in one labyrinth may suppress its activity and result in a physiological over-reaction from the opposing labyrinth or, secondly, there may be a release or lowering of pressure in the distended labyrinth so that this labyrinth temporarily is overstimulated and upsets the balance control of the other one. A significant point in this respect is the observation that, during an attack, the hearing in the affected ear may markedly improve. This second reaction is not a common one and has been noted only a few times. Between the acute attacks there is usually some deafness, the low pitched tinnitus continues, and the offending labyrinth is hypoactive to stimulation. Patients frequently complain of a sense of imbalance or unsteadiness between the active attacks and of a feeling of pressure or fullness in the head. In many cases the fear of attacks is almost as bad as the attacks themselves so that these people are afraid to venture outside of their homes.

No attempt is made here to explain the etiology or underlying causes of hydrops of the labyrinth which are still unknown. In my experience medical treatment has rarely been successful in curing this disease, although it often alleviates the symptoms and enables the patient to tolerate the condition. I do believe that conservative therapy should always be tried. There are many and varied forms of treatment advocated, which in itself is indicative of the lack of effectiveness of any one form of treatment. It is interesting to note that, knowingly or unknowingly, the accepted forms of treatment all seem to have as their aim a lowering of the distention of the labyrinth. These include the use of histamine, nicotinic acid, sodium elimination or replacement and dehydration. The efficacy of any new form of treatment must be regarded with question until a large number of cases have been treated and over a considerable length of time because of the possibility of a spontaneous remission of the symptoms characteristic of these cases. In my experience treatment with small subcutaneous injections of histamine has been most effective in alleviating this condition, with gratifying results in about one-third of the cases. There are many cases which do not respond to conservative therapy, and this condition is so incapacitating that the patients become desperate and are willing to gamble on any kind of surgical procedure which has a chance of eliminating this distressing malady. The economic

phase also deserves consideration as many of these patients are unable to work or earn a livelihood

Up to the present time the accepted surgical procedure for this condition has been sectioning of the vestibular nerve. It has been quite successful in a few expert hands. However, it is a hazardous undertaking and the results have sometimes been disappointing. Moreover, the low pitched grinding tinnitus is usually not alleviated, and some cases have cerebellar disturbances and difficulty with balance even though the acute, vertiginous attacks disappear. There is also the danger of injuring the facial nerve. Partial or total nerve section would seem to be an illogical procedure for this condition as it does not attack the seat of the trouble, namely, the hydrops of the labyrinth. I believe that any operation performed should be upon the labyrinth itself and should include opening the membranous labyrinth to release some of the endolymph. There have been few reports of labyrinth surgery for this condition. Portmann's<sup>3</sup> endolymphatic sac operation has relieved some patients, although the relief has often been only temporary and some of these cases had complete loss of hearing in the operated ear. In England the operation of choice until recently would seem to be alcohol injections into the labyrinth, either through the drum and oval window or through a trephine opening in the horizontal canal. This procedure causes complete destruction of the cochlea and vestibule and has not infrequently caused facial paralysis. It has found little favor in this country. Putnam<sup>4</sup> reported two cases in which he opened the superior semicircular canal by way of the middle cranial fossa and used a coagulating current to destroy the vestibule without destroying the cochlea. This procedure has merit but the approach is unnecessarily difficult and the cranial cavity need not be opened. In the past year Cawthorne<sup>1</sup> reported 50 cases in which, by way of the mastoid route, he opened the bony, horizontal semicircular canal and with fine tweezers removed the membranous organ. In some cases he also injected alcohol into the vestibule. In all of these cases there resulted a complete loss of both cochlear and vestibular function and the hearing was destroyed. However, his procedure has been received with favor because it has been effective in terminating the vertiginous attacks.

The ideal surgical procedure should be one which would be effective in terminating the vertiginous attacks and the tinnitus without destroying the hearing. This is one advantage of the partial nerve section operation since some of the hearing can be preserved.

The operative procedure which I am reporting is briefly as follows. A partial, simple mastoidectomy is performed by the postauricular route in which the mastoid antrum is opened widely and the outer wall of the aditus is removed far enough forward to expose the short process of the incus. With a small, motor driven burr the bony, horizontal semicircular canal is opened medial to the short process of the incus. The opening is made in this portion of the canal since it is near the ampulla and, through an opening at this point,

a needle can be passed forward through the canal into the vestibule. When the point of the needle strikes the anterior wall of the vestibule, it is then slightly withdrawn and pressed towards the medial wall so as to avoid the facial nerve. A light, coagulating current is then applied to the needle. The needle is withdrawn, a few "sulfa" crystals are dusted into the cavity, and the mastoid incision completely closed with clips. Clips are removed on the fourth day and the dressing usually discarded by the sixth day. I have employed this procedure on 11 cases of hydrops of the labyrinth in the past four years and I believe it gives promise of effectively terminating the vertiginous attacks and, at the same time, of preserving usable hearing in the operated ear. Nine of these patients had unilateral involvement and two had bilateral involvement. The elapsed time since operation has been from one to four years in eight of the 11 cases, and I believe sufficient time has elapsed for a true evaluation of results. In all cases to date the procedure has resulted in a complete loss of vestibular response to caloric stimulation of the operated ear. The hearing has varied markedly. In two cases there was total loss of hearing, but in one of these there was no attempt to preserve hearing as there was only residual hearing present before the operation. In four cases the hearing has remained at essentially the same level as before operation. Three cases show a further loss of hearing chiefly in the lower tones. Two cases show a marked improvement in hearing. In one of these cases, there was a uniform preoperative loss of hearing averaging 70 decibels, whereas, since operation, the hearing has returned to within normal limits and has remained so for two and one-half years. The nine patients with unilateral involvement have been completely free of vertiginous attacks since the operation. Some had almost immediate relief from vertigo, whereas in others it took from two to three months before the other labyrinth completely adjusted. The duration of postoperative vertigo and imbalance varied in direct proportion to the amount of labyrinthine activity in the affected ear before operation as shown by caloric tests. These nine patients have been rehabilitated and all have returned to their normal way of life and have been most grateful for the operation. Moreover, the low pitched, grinding tinnitus has been completely relieved in these cases although there has been little effect on the high pitched tinnitus which in some cases increased. None of these patients complained about the high pitched residual tinnitus. Three of them have stated that the pounding tinnitus before operation was as incapacitating as the vertigo. Using a noise apparatus to mask the hearing in the unaffected ear all nine cases could understand an amplified conversational voice with the operated ear. In other words they all have usable hearing in the affected ear. In the two bilateral cases, the desired results were not attained. Unfortunately, these were the two cases in which complete loss of hearing resulted in the ear operated upon so that it was considered too much of a hazard to operate on the second ear and they continued to have attacks from that ear, though one is responding to histamine and

gets along fairly well. I believe that the total loss of hearing in the operated ear of these two cases was due to technical mishaps during the operation, as a result of allowing a suction tip to come too close to the opening into the labyrinth in removing bone dust, with the result that the endolymph was entirely removed. I believe these mishaps can be avoided in the future. There were no postoperative complications in any of this series, all wounds healed by primary intention. Patients were well enough to be discharged from the hospital in from one to three weeks, depending upon the amount of postoperative physiological labyrinthitis in the unaffected ear.

In commenting upon the effect of this procedure I can only conjecture as to what actually happens inside the labyrinth. The original idea of using a coagulating current in the vestibule was to try to destroy the neuromechanism of the vestibule with as little damage as possible to the cochlea. The coagulating current may result in an actual coagulation of some of the endolymph. With a distended membranous organ, a needle passed into the vestibule would have to perforate the utricle. This mechanical perforation would cause a release of endolymph. Apparently the coagulating current tends to seal up again the opening in the membranous wall so that all endolymph is not lost and the cochlea can continue to function. It may be that the current destroys the nerve fibers of branches of the vestibular nerve to the utricle and superior semicircular canal which lie in the immediate vicinity of the end of the needle, while the needle itself has destroyed the horizontal semicircular canal in penetrating it. It is to be hoped that we may be able to obtain sections from some of these labyrinths for pathological examination at some future time.

#### COMMENT

No claim is made that this operative procedure is perfected. Nevertheless, our successes with it over the past four years make us believe that it is worthy of report, since it has proved successful in relieving the vertiginous attacks of Ménière's disease or hydrops of the labyrinth and has preserved usable hearing in nine of 11 cases operated upon to date. Animal experimentation and pathological examination of postoperative labyrinths are particularly desirable. The former is now being carried out by one of my conferees.

#### CONCLUSIONS

- 1 The term "Ménière's disease" should be used only to designate a hydrops of the labyrinth, a proved pathological entity.
- 2 This disease provides a clear cut, clinical picture which can be differentiated from all other conditions showing the Ménière syndrome.
- 3 The operative procedure here presented is still in its experimental stage.

4 The results in the above series of cases seem definitely to justify it as a surgical procedure for intractable cases of hydrops of the labyrinth

5 It has proved successful in terminating the vertiginous attacks in such cases

6 The effect on hearing has varied from restoration of normal hearing to a complete loss

7 The low pitched, pounding or grinding tinnitus has been eliminated by this procedure, although high pitched tinnitus has sometimes increased

8 This procedure seems to be preferable to that of sectioning the vestibular nerve in its results, simplicity and safety

#### BIBLIOGRAPHY

- 1 CAWTHORNE, J E The treatment of Menière's disease, Jr Laryngol and Otol, 1943, lviii, 363
- 2 HALLPIKE, C S, and CAIRNS, H Observations on pathology of Menière's syndrome, Jr Laryngol and Otol, 1938, liii, 625
- 3 PORTMANN, G The saccus endolymphaticus and an operation for draining the same for the relief of vertigo, Jr Laryngol, 1927, xlii, 809
- 4 PUTNAM, T J Treatment of recurrent vertigo by subtemporal destruction of the labyrinth, Arch Otolaryngol, 1938, xlviii, 161

# THE EFFECT OF DORYL (CARBAMINOYLCHOLINE) IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE\*

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CARBAMINOYLCHOLINE, known popularly as Doryl, is one of the most powerful parasympathomimetic drugs known. As a choline derivative, its properties causing general vasodilatation suggested its use in peripheral vascular disease. The literature is sparse with reference to its use in this connection. Starl,<sup>1</sup> in 1937, reported striking relief of rest pain except in the presence of gangrene or undrained purulent infection.

*Chemistry and Pharmacology*<sup>1,2</sup> Carbaminoylcholine chloride ( $\text{NH}_2\text{-COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{Cl}$ ) was first synthesized in 1932 by Kreitmair. Its actions parallel the effects produced by stimulation of the parasympathetic nerves such as general vasodilatation, drop in blood pressure, increased salivation, gastrointestinal peristalsis, uterine and vesical contractions, and sweating. In addition to the muscarinic effects of the drug, it also exhibits slight nicotinic effects on skeletal muscle and ganglion cells. Atropine neutralizes the muscarinic actions of the drug.

*Plan of Study* This is a three year study of a group of 21 patients who were given biweekly injections subcutaneously of 0.25 mg of doryl over periods varying from six months to three years. No patients with history or signs of asthma or chronic bronchitis were accepted for doryl therapy. The results of this treatment were compared with the results found in other controls receiving no specific therapy and studied for similar periods of time. Six additional controls were added to 30 others recorded in previous reports<sup>3,4</sup>. We thus had a total of 36 controls similar in diagnosis and complications to the treated group. All patients in both groups were ambulatory and had a complete general and peripheral vascular study prior to the onset of doryl therapy. All were instructed in foot hygiene and care, diet, and general measures outlined in our clinic routine. All patients were re-examined and studied at six month intervals according to the following criteria:<sup>5</sup>

I *Vascular Anatomic Status* This factor was determined by the evaluation of amplitude of vessel pulsation determined by palpation, temperature changes, rubor on dependency, pallor on elevation, and roentgen study for arterial calcification. This factor was graded from four plus, indicating severe involvement, to zero indicating no involvement.

\* Received for publication October 5, 1944.

From the Peripheral Vascular Disease Department, The Bronx Hospital, Bronx, New York.

II *Tissue Anatomic Status* This was determined by the degree of involvement of the superficial and deep tissues and graded four plus indicating presence of gangrene, three plus indicating ulceration, two plus indicating infection without gangrene, and one plus when skin atrophy, muscle atrophy or nail changes were present, zero when no involvement was apparent

III *Rest Pain* This refers to pain other than claudication. It includes neuritic pain, paresthesias, coldness or night cramps. This was graded four plus for severe pain, to zero for no pain

IV *Claudication* This was measured as an index of the number of blocks the patient could walk before pain in the calves supervened. Four plus indicated that the patient could walk only half a block, three plus indicated patient could walk one-half to two blocks, two plus indicated two to four blocks, and one plus indicated more than four blocks, zero indicated absence of claudication

V *Vascular Reserve* This was studied by means of the thermal vasodilatation test and complete nerve block (common peroneal and posterior tibial) where the first test failed to produce complete vasodilatation. Vascular reserve was graded four plus indicating full vasodilatation by production of a rise in skin surface temperature of the big toe to  $30.5^{\circ}\text{C}$ , three plus a 75 per cent rise from the initial temperature to  $30.5^{\circ}\text{C}$ , two plus a 50 per cent rise, one plus a 25 per cent rise, and zero negligible or no rise

VI *Functional Classification* This represents a composite evaluation of all factors

Class I Patients with organic disease without symptoms

Class IIa Patients with organic disease with minimal symptoms

Class IIb Patients with organic disease with moderately severe symptoms

Class III Patients with organic disease bedridden because of gangrene, infection or intractable pain

Class IV Patients with symptoms, without evidence of organic vascular disease

*Procedure* All patients who were placed on doryl therapy were first subjected to the following precautionary study. 0.125 mg of doryl was injected subcutaneously and pulse and blood pressure readings were taken at five minute intervals for 30 minutes. If no untoward effects were noted, the study was repeated with a dose of 0.25 mg of doryl subcutaneously. If there were still no untoward effects, patients were started on 0.25 mg of doryl\* subcutaneously biweekly. A loaded syringe with atropine sulfate gr 1/100 was kept on hand for emergency use

\*We first used aqueous doryl containing 0.25 mg per cc for the subcutaneous injection. We then attempted to prolong the effect by preparing stock solutions of doryl in oil at a concentration of 0.25 mg per 0.50 cc. for subcutaneous injections. This method was found dangerous because of the insolubility of doryl in oil. Several patients resultantlly received an overdose of doryl with the following reactions: fainting, bradycardia, marked drop in blood pressure, marked intestinal peristalsis, salivation and sweating. These effects were immediately counteracted by the subcutaneous injection of atropine sulfate gr 1/100. At this



## RESULTS

*I Six month study* After treatment with doryl for six months, three patients showed no improvement in vascular or tissue anatomic status, and no improvement in vascular reserve. Claudication was improved in two cases. None of these three patients had rest pain before or after completion of therapy. Of 14 control cases observed over a similar period, eight cases showed improvement of vascular anatomic status, three cases showed improvement of tissue anatomic status, six cases showed improvement of vascular reserve. Claudication was not improved. Rest pain was improved in two cases. Functional status was not improved in any case.

It will be noted that for this period results were promising only with regard to claudication in the doryl treated cases.

*II One year study* After treatment of seven cases for one year with doryl, no cases showed improvement of vascular anatomic status, one showed improvement of tissue anatomic status, three cases showed improvement in vascular reserve. Rest pain was improved in three out of four cases. Two cases showed improvement in claudication. Functional classification was essentially unchanged in this group. Of 19 control cases, four showed improvement in vascular anatomic status, one in tissue anatomic status, six in vascular reserve, five in claudication, four in functional status. Only one out of 16 manifesting rest pain showed improvement in this category.

Results in the group treated for one year suggest definite improvement in rest pain and equivocal improvement in vascular reserve in the doryl series.

*III One and a half year study* Of three cases under doryl therapy for one and a half years, none showed improvement in vascular or tissue anatomic status. One case was improved in vascular reserve, one showed improvement in claudication, and two cases in this series complaining of rest pain prior to the onset of therapy had no rest pain after therapy was completed. One case showed functional improvement. Of 12 controls, four showed improvement in vascular anatomic status, four showed improvement in tissue anatomic status, five showed improvement in vascular reserve, and six showed improvement in claudication. There was no case of improvement in rest pain where it was present in 10 of the 12 control cases. Six cases showed functional status improved.

Results in the one and a half year group suggest relief of rest pain as the only benefit from doryl therapy.

*IV. Two year study* Six cases received doryl therapy for two years. Of these, one showed vascular anatomic improvement, one showed tissue anatomic improvement, three showed improvement in vascular reserve, one in

point, the idea was conceived of dissolving doryl in gelatin, in a liquid state which would form a slight nodule when injected subcutaneously (0.25 mg doryl per 0.5 cc of gelatin mixture). The nodule would disappear in 24 hours. There was no further trouble with this method which was used until September 1943 when gelatin was no longer obtainable because of the war. At this point we reverted to the use of aqueous doryl 0.25 mg per 0.5 cc. for the balance of the study which ended six months later.

claudication, and none in rest pain (only one patient in this group had rest pain) None showed improvement in functional status One control case showed no improvement in any category

This group suggests improvement in vascular reserve when doryl was given over a two year period

*V Three year study* Two cases continuing under doryl therapy for three years showed no improvement in any of the categories studied None of the control cases continued beyond two years

*Complication and Special Study* One patient, 67 years old, developed typical peptic ulcer symptoms while under doryl therapy The diagnosis of duodenal ulcer was confirmed by roentgen-ray Doryl therapy was discontinued because of the possible relationship A study of this factor was undertaken with 10 patients who were given fractional gastric analyses following alcohol test meal, and again following alcohol test meal plus a doryl injection of 0.25 mg immediately after the alcohol meal Specimens were taken during fasting, one-half hour after test meal and one hour after test meal The same intervals were used for the doryl sitting In two cases there was a significant difference in the free acid and combined acid determinations one hour after the beginning of the test The half hour extractions failed to show significant differences in any of the 10 cases Table 1 below illustrates the positive findings in the two cases

TABLE I

	Alcohol Test Meal			Doryl Alcohol Meal		
	Fasting	30 min	60 min	Fasting	30 min	60 min
(1) Free HCl	0	54.0	43.6	8.8	40.0	67.0
Combined Acid	13.6	67.2	59.8	20.8	80.0	107.0
(2) Free HCl	14.0	36.0	35.0	0	20.0	72.0
Combined Acid	34.0	70.0	65.0	15.8	36.0	98.0

*Summary* A group of 21 patients was studied from six months to three years while receiving biweekly subcutaneous injections of 0.25 mg of doryl It was found that compared with the control group of 36 cases, there were no significant differences in vascular anatomic status, tissue anatomic status, claudication, vascular reserve or functional classifications Where, however, the control group had no improvement with regard to rest pain doryl treated cases showed a definite relief of rest pain

### CONCLUSIONS

Doryl is a valuable drug whose application to peripheral vascular disease should be limited to the treatment of rest pain It is contraindicated in patients with history or symptoms of peptic ulcer or asthma Doryl should

be used only by those who are thoroughly acquainted with its pharmacology and its contraindications

We gratefully acknowledge the technical assistance of Rosa Abraham, and the volunteer secretarial assistance of Leah Banks. Appreciation is also extended to Dr H Feibes of the Department of Gastroenterology for his assistance in the gastric analyses

#### BIBLIOGRAPHY

- 1 STARR, I    Carbaminoylcholine (Doryl or Lentin)    Its action on normal persons in peripheral vascular disease, and in certain other clinical conditions, *Am Jr Med Sci*, 1937, cxciii, 393
- 2 GOODMAN, L, and GILMAN, A    The pharmacological basis of therapeutics, 1943, Macmillan Company, New York, p 367
- 3 ZURROW, H, SALAND, G, KLEIN, C, and GOLDMAN, S    The effect of testosterone propionate in the treatment of arteriosclerosis obliterans, *Jr Lab and Clin Med*, 1942, xxviii, 269
- 4 KLEIN, C, SALAND, G, and ZURROW, H    Pancreatic tissue extract (insulin-free) in the treatment of peripheral vascular disease, *Ann Int Med*, 1943, xviii, 214
- 5 SALAND, G, KLEIN, C, ZURROW, H, GOOTNICK, A, and KATZ, A    Criteria for the classification and diagnosis of peripheral vascular diseases, *Arch Int Med*, 1940, lxxv, 1035
- 6 SALAND, G, KLEIN, C, and ZURROW, H    The thermal reflex vasodilatation test in peripheral vascular disease, *Am Heart Jr*, 1939, xvi, 581
- 7 GOOTNICK, A, SALAND, G, KLEIN, C, and ZURROW, H    Studies on vasodilatation tests in peripheral vascular disease, *Jr Lab and Clin Med*, 1942, xxvii, 878

# THE INTEGRATION OF THE EXACT SCIENCES IN ALLERGY RESEARCH \*

By LESLIE N GAY, M D , F A C P , *Baltimore, Maryland*

SOME years ago Dr Abraham Flexner of the Rockefeller Institute, in conversation with the late Mr George Eastman, asked him whom he regarded as the most useful worker in science in the world Mr Eastman replied without the least hesitation, "Marconi" Dr Flexner surprised him by saying, "Whatever pleasure we derive from the radio or however wireless and the radio may have added to human life, Marconi's share was practically negligible" Mr Eastman, a far-seeing and philanthropic gentleman, was planning to devote his vast fortune to the promotion of education in useful and exact sciences He asked Dr Flexner for an explanation, and I quote Dr Flexner's clearly thought out reply "Mr Eastman, Marconi was inevitable The real credit for everything that has been done in the field of wireless belongs, as far as such fundamental credit can be definitely assigned to anyone, to Professor Clark Maxwell, who in 1865 carried out certain abstruse and remote calculations in the field of magnetism and electricity Maxwell reproduced his abstract equations in a treatise published in 1873 Other discoveries supplemented Maxwell's theoretical work during the next 15 years Finally, in 1887 and 1888 the scientific problem still remaining—the detection and demonstration of the electromagnetic waves which are carriers of wireless signals—was solved by Heinrich Hertz, a worker in Helmholtz's laboratory in Berlin Neither Maxwell nor Hertz had any concern about the utility of their work, no such thought ever entered their minds They had no practical objective The inventor in the legal sense was of course Marconi, but what did Marconi invent? Merely the last technical detail, the now obsolete receiving device called a coherer, almost universally discarded"

What is true of the research of Heinrich Hertz may be said of the investigations of scientists the world over Without electricity the world today would be helpless Michael Faraday's discoveries of the induction of the electric current and the effect of magnetism on polarized light, together with even earlier studies in the field of electricity, have led to many practical applications of electricity by which our daily burdens have been lightened In the domain of medicine and public health the principles of electricity have been utilized to great advantage to relieve suffering humanity For example, one can mention the application of electricity to the production of the roentgen-ray so helpful in the diagnosis of disease, and more recently, in the treatment of inoperable cancer

Until the onset of the present tragic conflict scientists throughout the

\* Received for publication July 24 1944

world have utilized, wherever possible, the discoveries of their peers, in order to solve their problems and to advance their theoretical hypotheses. This is true in medicine, a science which is made up of many separate fields awaiting research and investigation. As in the case of Marconi, so aptly discussed by Dr. Flexner, the clinician frequently adapts the scientific discovery of the laboratory investigator to the more practical side of medical science, and although I do not reflect critically on the ability of the clinician, who recognizes "the usefulness of useless knowledge," nevertheless more honor is due to the research student.

For the past 20 years I have been analyzing a branch of medicine which was given the name of "Allergy" by von Pirquet in 1906. This term is synonymous with the more explanatory word "hypersensitiveness." It refers to the condition of an individual who reacts specifically, and with char-

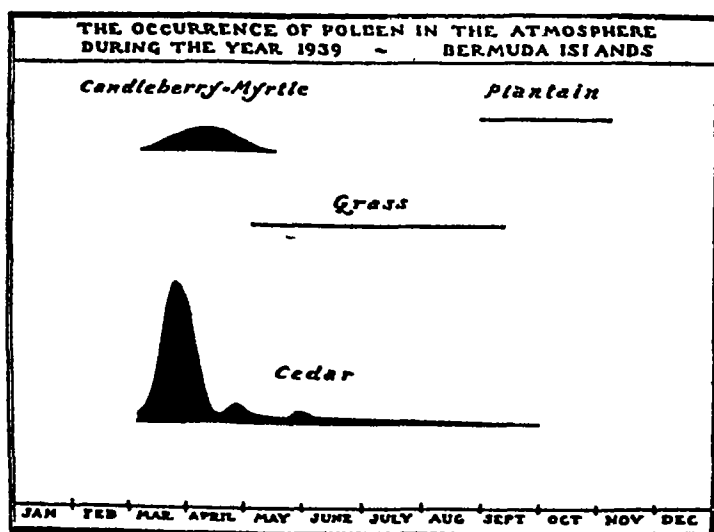


FIG 1 Bermuda survey

acteristic unusual symptoms, to contact with, or the administration of, a substance which when given in similar amounts to the majority of other individuals proves harmless (Louis Tuft, 1937). An example, the ingestion of egg white in most individuals produces no ill effects, but in a small number of persons violent reaction may occur even though the amount ingested is of microscopic size. Allergy is recognized through such common symptoms as those which are associated with hay-fever, asthma, hives, eczema, poison ivy, and other skin inflammations resulting from contact with primary or sensitizing irritants.

It is my purpose briefly to outline the relationship of the more exact sciences to this medical specialty and to demonstrate by these deductions how dependently related are the sciences in fields which might seem extremely remote one from the other. In order to study the many problems with which I have been confronted it has been necessary to resort to the knowledge dis-

closed by the botanist, the chemist and biochemist, the immunologist and physician of public health, the mechanical and electrical engineer, the industrialist, and more recently the legal profession

It is quite impossible here to discuss in detail this remarkable specialty, which, by necessity, has applied so many diverse sciences to the solution of its problems. The greater part of our knowledge of those manifestations of human hypersensitiveness, grouped under the general term of *allergy*, is based upon the fundamental principles of anaphylactic reaction in lower animals. Anaphylaxis, demonstrated in 1904 by Dr Theobald Smith, is a term applied to a state or condition which is produced by the following experiment. If a small amount of horse serum, perhaps 0.1 cubic centimeter, is injected into a normal guinea pig, no reaction will occur. If, however, after an "incubation" period of 14 days, a second larger amount (1 cubic centimeter) of horse serum is injected into the vein, the animal will show characteristic symptoms and usually will die in a very few minutes. The reaction thus produced is termed *anaphylactic shock*. Although human allergy and animal anaphylaxis resemble one another, there are two distinct and fundamental differences. First, human allergy may be inherited whereas animal anaphylaxis is artificially induced in the laboratory, second, in animal anaphylaxis the repeated injection of very small doses of the sensitizing serum will prevent the shock or death of the animal. Complete desensitization in human allergy on the other hand is most difficult and is rarely accomplished.

An excellent example of the serious reaction occasionally encountered in man is to be found in the prophylactic treatment of tetanus. It is common knowledge that any puncture wound should be looked upon as a potential case of tetanus. As a preventative it has been the universally accepted practice to give an injection of tetanus antitoxin. For years the antitoxin has been developed through the medium of horse serum. Consequently, the individual who might have inherited a sensitivity to horse serum has a violent and distressing shock reaction immediately after the prophylactic injection. Fortunately, in the majority of such instances serious results can be combated by appropriate medication. Nevertheless, these serious and occasionally fatal reactions have stimulated the biologist and biochemist to greater efforts in research and, fortunately, during the past decade the solution of the problem has been found. Tetanus toxoid has been developed without horse serum (the offending agent) and ample opportunity to test its effectiveness has been offered during the present war.

The procedure of administration differs somewhat from that which was followed in the prophylactic treatment with the antitoxin. In the latter case the antitoxin was administered after the wound had been incurred. The present method of prevention of tetanus in our armed forces is to administer a dose of toxoid immediately upon the induction of the soldier into the service, to be followed by a second dose after two months. Should the

soldier later receive a wound, his identification tag will state he has received preliminary prophylaxis and only a third supplementary dose will be necessary as soon as it can be conveniently injected. The success of this preventive treatment has been recently reported by the British and French armies. In the British Army the prophylactic treatment prior to Dunkirk was optional on the part of the soldier, but in the French Army the treatment was compulsory. Among 16,000 wounded British soldiers who had received prophylactic injections no tetanus occurred, while in 1,800 wounded who had refused treatment there were eight cases. On the other hand, among the thousands wounded in the entire French Army, all having received toxoid, but one case of tetanus developed.

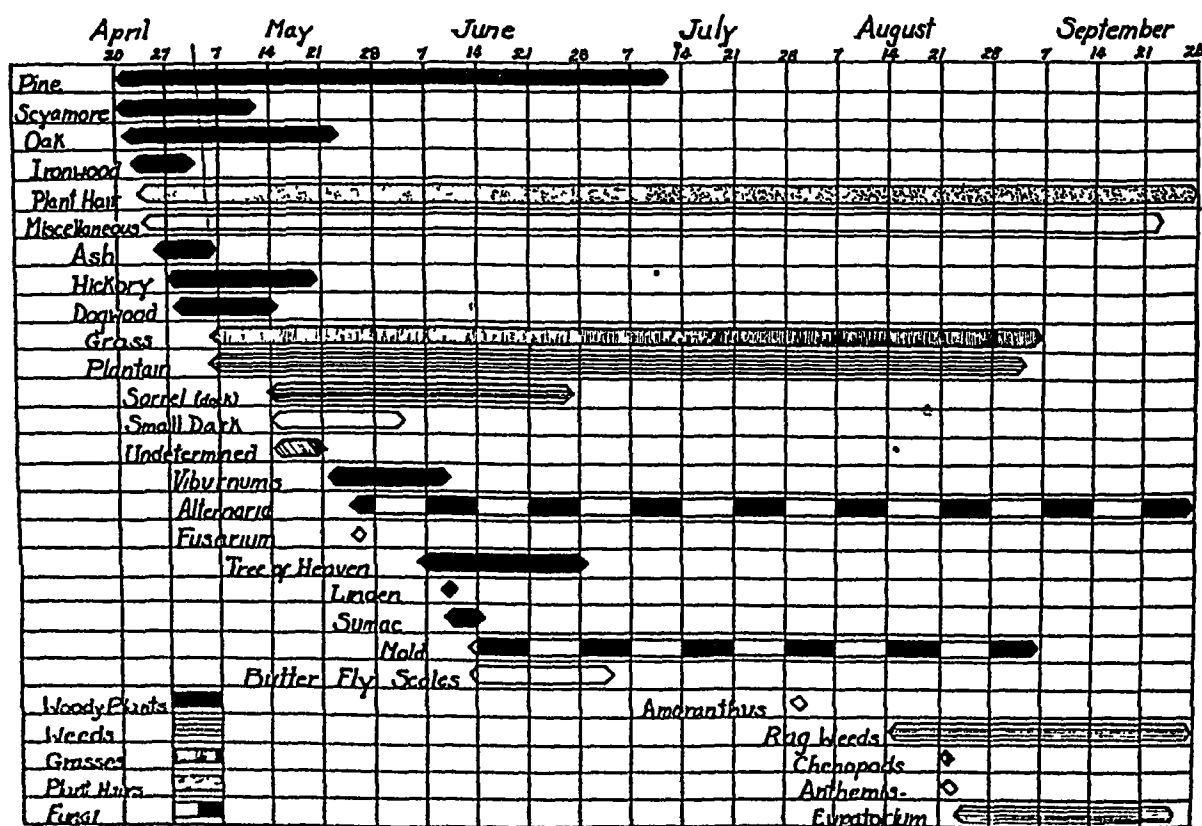


FIG 2 The occurrence of pollen in the atmosphere during the year 1932, Baltimore, Maryland

After the demonstration of anaphylaxis in animals, it was a natural development for the clinician to attempt correlation of the phenomenon with certain symptoms observed in the human subject. It was not until 1910 that the attention of immunologists was directed by Meltzer to the similarity of the marked distention of the lungs seen in the guinea pig and the pulmonary distention seen in patients with bronchial asthma. However, it was in 1819, nearly a century earlier, that Bostock, an English physician, described a syndrome which is a classical example of hypersensitiveness. I refer to the disease commonly spoken of as hay-fever. Bostock described this syndrome

as "summer catarrh" with a seasonal incidence and a distinct symptomatology Elliotson, in 1831, referred to the fact that one of his patients developed the symptoms when flowers were in bloom, with the inference that the symptoms were due to pollen This is the first reference in medical literature of this possibility It remained for Blackley to confirm this supposition by a series of experiments, published in 1873 He was the first to apply the skin test, inoculating his own skin with dry pollen by the scratch method, and being a victim of this group of symptoms he obtained a large hive at the site of the impregnated area

Since the excellent publication of Moore and La Garde in 1926, entitled "The Identification of Pollens from So-Called Hay-Fever Plants," in the *Annals of the Missouri Botanical Garden*, American allergists have given increasing attention to the pollen content of the air and to its relation to the incidence of hay-fever and asthma, and systematic surveys have been carried out in many sections of the United States It was in 1929 that Acquarone and Gay published the first survey of the pollen flora of the Eastern Seaboard Ordinary microscope slides, greased lightly with vaseline, were exposed out of doors These slides, protected by a small metal shelter open at the sides, were collected after twenty-four hours' exposure and the number of pollen grains of each species of tree or plant was counted and identified The keys developed by Moore and La Garde proved of great value in making identifications It is obvious that pollen grains, which appear on the slides in considerable numbers, must be liberated from the freely flowering vegetation prevalent in the neighborhood One has only to note what species are pollinating abundantly and to secure pollen of each directly from the anthus in order to obtain standards for comparison with those deposited on the slides Pollen grains, the microspores of seed plants, possess, in common with plant spores in general, a high degree of specificity, that is, each species possesses distinctive spores Since the characteristics of the spores are so definitely fixed in each species, it is possible to identify pollen grains with reasonable certainty

The pollen season falls naturally into four subseasons The tree season, March and April, the grass season, May, June, the plantain season, June, July, and the ragweed season, August and September As a patient's clinical symptoms will parallel these seasons, it is quite easy to determine from the history which species of pollen is responsible for the discomfort Confirmation of the cause is established by the intracutaneous or scratch test Since 1929 an annual survey has been carried out in the Baltimore area and the schematic charts demonstrate the distribution qualitatively of the pollen in the atmosphere during the flowering seasons

In spite of the knowledge obtained from the survey of the pollen flora, it is often impossible to relieve a patient who suffers from the symptoms associated with pollen inhalation by the usual specific treatment A haven of refuge for those who suffer from the distressing symptoms which result



from the inhalation of dry, wind borne pollen, has been sought for many years by patients in advertised areas of this continent. For a time the New England State, New Hampshire, seemed to answer all requirements, as civilization has moved into the secluded mountainous areas, many seeds of the offending grasses and ragweeds have been implanted in the fertile soil by the traveling public, and consequently there has been a decided "dropping off" in the popularity of the White Mountains as a region where those who suffer with these respiratory symptoms may find relief. Farther to the west, in Northern Michigan and in Southern California, one may sojourn in comparative comfort during the ragweed season. But other complicating factors, which are as disturbing as the ragweed pollen, may be encountered in these districts.

It is recognized that the continued influence of pollen on the mucous membrane of a sensitive individual depends upon several factors, such as temperature, barometric pressure, rainfall, prevailing winds, and the relationship of the land to the sea. Prevailing winds proceeding from the ocean cleanse the atmosphere, and, therefore, the relative location of land to sea is by far the most important factor in reducing to a minimum offensive pollen grains. This is true irrespective of the season of the year.

Because of their popularity with, and their accessibility to the citizens of the United States, the islands of Bermuda were chosen for a survey of the flora of the atmosphere. In the Bulletin of the Johns Hopkins Hospital, issued February, 1941, a report of the survey can be found.

In size the group of islands is slightly over 19 square miles, 15 miles long and three miles wide, the average width is somewhat less than one and a half miles. The average depth of soil on the islands is estimated to be six inches. The climatic conditions of Bermuda produce subtropical or warm temperature vegetation. Spring is the blossoming season for most annuals, but in the hottest days of August and the coldest days of January and February there are blossoms in every garden. Although there is a profuse growth, it is remarkable that only 87 per cent of the plant life is endemic. The large proportion has entered by natural agencies from America and the West Indies.

Because of the geographic and climatic advantages which seemed to be offered in Bermuda for the relief of pollen-sensitive patients, a survey of the pollen flora of the atmosphere suggested itself. A single season's record of the succession of species of pollen which invade the atmosphere of any given locality furnishes valuable information regarding its hay-fever potentialities. Each year the cycle faithfully repeats with only such minor fluctuations as may be due to seasonal variations. The survey was commenced March 1, 1939, and was concluded April 1, 1940. The same procedure described by Acquarone and Gay in 1929 was followed.

The conclusion is that there is available within easy travel distance of the United States a group of islands which has a constant year-round atmosphere

entirely free of the usual disturbing pollens of grasses, plantain and ragweed. Only during late February and March are there two trees, cedar and candleberry myrtle, which produce sufficient pollen to cause the respiratory symptoms of hay-fever and pollen asthma. The absence of the pollens so disturbing to countless citizens of the United States should make the Bermuda islands most popular during the spring and summer months.

The specific treatment of persons sensitive to pollens, namely, injections of the extract of the offending pollen in graduated doses, may fail to give the desired relief. It was essential, therefore, to try to find another means to bring comfort to these patients. An opportunity was afforded by a manufacturer of air-conditioning equipment to study the effect of air-conditioned atmosphere on individuals suffering with symptoms of hay-fever and pollen asthma. This treatment was a new method of approach and the results of the investigation were published in the *Journal of the American Medical Association* in May, 1933. The efficacy of the air-conditioning system used in the investigation was demonstrated most satisfactorily. Complete relief was given to patients suffering with hay-fever while they occupied the air-conditioned room. It was emphasized, however, that the relief of patients depends entirely upon the ability of the equipment to cleanse the atmosphere of offending pollen, the cooling feature is quite secondary, and is important only as a means to accomplish more perfect filtration and lend physical comfort to patients while occupying such an equipped room. To those individuals who can afford to install such a system, whether in the home or in the office, great relief can be assured.

After the demonstration that pollen can be filtered from the atmosphere by the use of air-conditioning units, other mechanical devices were sought to accomplish the same result. In 1935 Crip, of the University of Pittsburgh, published the clinical results which he obtained after he had "cleaned" the pollen from the air with an electrostatic unit developed by G. W. Penney. The unit was inexpensive and was designed to supply and clean 27,000 cubic feet of air per hour. The electrostatic air cleaner removes dirt and pollen by generating electrons in a high electrostatic field. These electrons tend to attach themselves to dust particles, thus giving the particles a negative electrical charge. When they touch the positively charged surface of a series of plates, the electrical force disappears and they are held by adhesion. This method efficiently removes pollen from the atmosphere, although its original purpose was to clean from the atmosphere minute copper particles, which often endanger workmen in industrial plants.

Respiratory distress of a violent type frequently results from a dust hazard little suspected by the average physician, and certainly not suspected by the engineer who originally designed the pipeless furnace method of house heating. It consists of one large central hall register through which hot air passes and distributes both dust and imperceptible gas from the first floor to the attic. Unfortunately its popularity because of its cheapness has been

widespread throughout the farming districts and small country towns. It is one of the common causes of winter asthma in both the child and the adult and must be looked upon as a serious health hazard. Relief of the asthmatic tendency is obtained after the removal of the "hot-air" system of heating.

Often patients subject to attacks of asthma, which develop from so many different causes, fail to respond to any of the commonly used therapeutic measures. Fortunately the physicist and mining engineer have contributed to medical science a chemical element, helium, which is most effective in relieving the asthmatic paroxysm. The story of helium is unique in the annals of science. Until 15 years ago it was obtainable only in very small quantities and then at the price of \$2,500 a cubic foot. Today for about one cent a cubic foot an unlimited supply is available.

It was Sir Norman Lockyer who, by his development of spectroscopic investigation (Proceedings Royal Society, vol. 15, 1866) as applied to astronomy, established the fact that the sun spots are large magnetic centers and the prominences are masses of incandescent gas, mainly hydrogen, forming an envelope about the sun, the thickness of which is estimated to be 5,000 miles. A little more than 70 years ago, in 1866, this scientist while investigating the spectrum of the sun observed that eruptions from its surface gave bright lines in the yellow zone that were hitherto quite unknown in the sun or the laboratory. He was convinced that they were due to some substance in the sun unknown to the earth and for which he coined the name "helium," deriving it from the Greek name for the sun (*Helios*). He announced his discovery in October, 1868.

Lockyer's observations were made without the advantage of an eclipse of the sun. It is interesting that Janssen, a distinguished French astronomer, observing eruptions from the sun's limb in India in 1868 during a total eclipse, arrived quite independently at Lockyer's conclusion, and wired the French Academy of Science that he was of the opinion that the protuberances were composed of a gas that emitted the yellow spectral lines he had seen. Because of this joint discovery, announced coincidentally on the same day, one in England, the other in France, the French Academy had a medallion struck in 1868 commemorating it, bearing relief profiles and names of Lockyer and Janssen. There the subject rested until 1895 when William Ramsay freed a gas from the mineral cleveite and found in its spectrum the brilliant yellow line due to helium. Thus finally the gas was identified as a constituent of the earth and analysis revealed that it was a member of a group of gases known as non-reactive elements. Neon, used in "neon" street lights, is also of this group. These gases are colorless, noninflammable and nonexplosive. Next to hydrogen, helium is the lightest known substance, and is liquefied with the greatest difficulty.

Practical application of helium was delayed for many years until it was discovered in conjunction with natural gas in large quantities in the United States. A few small deposits were found in Kansas in 1903 and in 1928

the great wells near Amarillo, Texas, were discovered. Our government has since stored millions of cubic feet of the refined gas for military and commercial uses.

One of the most important and recently adopted uses for helium is in deep sea diving and caisson construction\*. When a diver descends into the sea, or when a man is at work in a caisson, increased amounts of air are taken up by the body tissues, and because air contains 20 per cent oxygen and 80 per cent nitrogen, the absorption of nitrogen is particularly large. When the pressure is reduced, the excess amount of oxygen can be readily taken care of in the body tissue by ordinary combustion, but the nitrogen excess tends to separate and form gas bubbles.

If a diver is raised or "decompressed" too rapidly, he may develop "caisson" illness or the "bends," characterized by severe body pain, unconsciousness and even death, as was observed by Paul Best in 1878. It is necessary, therefore, to raise the diver slowly until the nitrogen has had time to escape through the lungs during respiration. The usual time necessary for a diver to descend to a depth of 200 feet is three to eight minutes, but after remaining at this level for 45 minutes, at least two hours will be required to bring him to the surface without distressing illness. Since Hildebrand knew that helium is the least soluble gas, the idea occurred to him to substitute helium for nitrogen in the gaseous mixture for divers to breathe. The sinking of a submarine with the loss of an entire crew suggested to our Navy that by analyses and research our physicists could enhance the usefulness of this gas. Hildebrand's impressions were confirmed. Because of its high rate of diffusion, moving three times more swiftly than nitrogen, it is liberated with greater rapidity from the lungs, thus proving its usefulness during the "decompression" of deep sea divers. Its practical application was assured and demonstrated when helium played a major role in the rescuing of our sailors from the *Squalus* submarine disaster.

The use of helium mixed with oxygen as a therapeutic gas was reported by Alvan Barach in 1934. He suggested its applicability in the treatment of asthmatics. Substituting helium for nitrogen in the air, the specific gravity of this mixture compared to that of the air is 0.34. The rate of diffusion of helium is three times that of nitrogen and the molecular weight is 4, while that of nitrogen is 28. Since respiratory work is in general proportional to the pressure of the air, the physical effort by the patient or the pressure required to move helium-oxygen mixtures in and out of the lung, should be decidedly less than that incurred when breathing nitrogen-oxygen (air) mixtures. Striking diminution in the respiratory effort of an asthmatic patient is observed immediately when a mixture of helium and oxygen is inhaled. The vicious circle caused by lack of oxygen and respiratory

\* Professor J. H. Hildebrand, of the University of California and Drs. R. R. Savers and W. P. Yant of the U. S. Bureau of Mines, published a comprehensive treatise on this application in 1928.

fatigue is interrupted and, equilibrium being restored, the life of the patient may be saved

We are living in an age which demands the prevention of disease rather than its cure. New methods of industry have rapidly developed, and new products have required in their manufacture the most complex chemical agents. Consequently the industrialist has encountered among his workmen manifestations of diseases which 20 years ago rarely presented themselves to a physician. Industry has been conscious of the hazards of these processes and is well aware that efforts must be made to eliminate them. I wish to refer briefly to industrial diseases, many of which may be classified under the head of "contact dermatitis."

Since the founding of the School of Hygiene at The Johns Hopkins University in 1918 the prevention of disease has been most emphatically impressed upon the physician, and indirectly upon the industrialist. Students from all parts of the world have learned how to combat and control epidemic diseases and also how to safeguard employees from hazards in occupation. Industrial medicine has attained a position of great importance, and management now recognizes the advantages of healthy personnel. The most prevalent industrial disease today is an inflammation of the skin termed "contact dermatitis." It is by no means a new problem, for as early as 1700 Bernardino Ramazzini published a compilation of industrial diseases, mentioning the swollen hands of the baker due to wheat flour and the itch which developed from the dust of cereal infected with a then invisible parasite. Even today "grain itch" is very common among the handlers of wheat, rye, corn and linseed meal, if these cereals harbor their minute parasites. Scattered contributions have appeared in the literature on the subject since 1900. In 1928 the United States Public Health Service created a special department for the study of occupational dermatitis and named Dr. Louis Schwartz as its director. This is an important office, as 70 per cent of all occupational diseases are due to skin injuries.

There is a curious predisposition to occupational dermatitis. Dark-skinned racial groups have proved less susceptible to skin irritants, this being well illustrated by the negro. Certain individuals unfortunately have skin characteristics which predispose them to irritants. A dry skin can not withstand the action of alkalis and solvents as well as a thick oily skin, on the other hand, an oily skin is more susceptible to the action of tar, pitch and petroleum products.

The chemical agents which cause occupational dermatitis may be divided into two groups, the primary irritants and the specific irritants. The chemicals which will produce an inflammation on any skin if allowed to remain in contact in sufficient concentration for the necessary length of time comprise the first group and the second is composed of those which affect a comparatively small number of workers only after they have been sensitized or have become allergic to the irritant following previous exposure.

The primary irritants are both organic and inorganic—alkalis, acids, solvents, essential oils, dye intermediates, tar, pitch and petroleum products. From these irritants the industrial workers constantly require protective measures.

The specific sensitizing irritants likewise are numerous, and are encountered in such industries as those which employ the furrier, the dyer, the weaver, the leather worker, the oil worker, the manufacturer of cosmetics, the painter, the worker in plastics, and in many other trades. Especially among the fabric dyers and handlers of plastics, the use of complicated and synthetically prepared compounds adds to the difficulty of tracing the offending agents. Recently it has been discovered that certain chemicals, which come in contact with the skin or which gain access into the circulating blood by ingestion, may produce an unusual pigmentation because of the phenomenon of photosensitivity. Exposure to light produces such a change in the character of the material on or in the skin that it may be extremely irritating. A striking example is found among the men who work with pitch in the conduit industry. Exposure to sunlight produces an inflammation with pigmentation of the skin. As long as the worker remains indoors no serious reaction occurs. Recovery from the disease depends upon the use of protective clothing, even though the irritation diminishes the pigmentation is usually permanent.

CHART I  
Chemical Primary Irritants  
General Irritants

<i>Inorganic</i>	Acids and Salts	Sulphuric Nitric Arsenous Etc	Alkalis	Sodium Hydrate and Carbonate Potassium Hydrate and Carbonate Etc
	Salts of Irritant Metals	Mercury Chromium Arsenic Etc		(Sensitization Usually an Important Factor)
<i>Organic</i>	Acids Anhydrides and Salts of	Acetic Carbolic Formic Oxalic Picric Salicylic Etc	Solvents	Hydrogenated Phenols Turpentine Formaldehyde Xylol Chloroform Etc

CHART II

Specific Irritants Which Cause Dermatitis in Those Sensitized by Previous Exposure

Explosives	Photo Developers	Biologic Agents
Cosmetics	Soaps	Bacteria
Oils (Vegetable and Mineral)	Rubber Compounds	Parasites
Fur Dyes	Insecticides and Fungicides	Fungi
Leather Dyes	Fabric Dyes	
Photosensitizers	Resins and Waxes	

A similar reaction occasionally is precipitated after the ingestion of the barbiturates and with the addition of the sulfonamides another source of photosensitivity has been encountered

It has been suggested that this unusual reaction is produced by changes in the physiologic porphyrin present in the skin, although other factors are probably involved

The prevalence of occupational dermatitis has necessitated rigid and careful examination of prospective employees. If an individual is "sensitive" or allergic to a chemical agent which can not be avoided in a chosen occupation, he should not be subjected to a hazard which might incapacitate him for weeks. By a simple test, known as the "patch test," many industries determine whether a new worker can safely handle sensitizing irritants. A small amount of the chemical is placed on the skin and a fluff of cotton is placed over it, held firmly by means of non-irritating adhesive. Within 48 to 72 hours, the area is examined, and if the worker is likely to have trouble from contacts associated with his new occupation, a characteristic red vesiculating eruption will be observed under the adhesive. It would be extremely unfortunate for this individual if he were employed in such an environment.

As a consequence of these unusual features associated with contact dermatitis, certain criteria have been prepared as a guide to industry by the American Society of Dermatology and the American Board of Allergy. It has been necessary to have them because of the confusion which has arisen in the minds of the legal profession in compensation decisions. Gross negligence in the protection of workmen from well known primary irritants should entitle them to compensation, but there is a grave doubt as to whether they should be compensated for some hereditary or allergic defect for which no employer is responsible.

In this brief discussion I have outlined the ramifications of a minor specialty of medical science, allergy, with the more exact sciences. If one desires to advance in a chosen field, regardless of the specialty, a broad horizon is open to the student of research as well as to the clinician. Neither can accomplish the ultimate without a knowledge of development and progress in other fields. The association of members of a university faculty, the teaching of graduate students, and the instruction of undergraduates all tend to stimulate us to freedom of thought. So long as this freedom is defended and maintained, there need be no limit to scientific progress.

# THE CLASSIFICATION AND NOMENCLATURE OF LEPROSY WITH SUGGESTIONS FOR A SIMPLIFICATION OF BOTH

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THE classification of leprosy has had two almost wholly independent origins, one largely clinical, the other largely biological, and both in part bacteriological. The two have never been reconciled with each other, principally because the clinical leprologists and the dermatological leprologists have never learned to speak one another's language. This linguistic barrier is a remarkable one, the importance of which has not been fully appreciated. It has frequently stood, not only between these two different groups of students of leprosy, but also between the clinical leprologists and their own understanding of the disease.

In an attempt to remove this barrier, we will consider the problem under the following headings: (1) the clinical classification of leprosy, (2) the dermatologic classification of leprosy, (3) the South American dermatologists' classification of leprosy, and (4) leprologic nomenclature. It is our thesis that there is no fundamental incompatibility among these three classifications, and that they can be reconciled with one another, and greatly simplified, by little more than a change in the nomenclature.

## THE CLINICAL CLASSIFICATION

The older clinical classification of leprosy, as described by Morrow<sup>1</sup> in 1894, divided the disease into two forms according to its localization: "tubercular" (or "tegumentary") if the skin and mucous membranes were the site of most of the lesions, and "anesthetic," "trophoneurotic" or "nerve" leprosy when it involved primarily the peripheral nerves. He added that "the two forms exhibit marked differences in their external characters, mode of evolution, course, and termination." By 1910, according to Stclwagou,<sup>2</sup> the names "tubercular" and "anesthetic" had become established, in dermatologic literature at least, as the names for these two varieties of the disease, though Ormsby<sup>3</sup> more recently advocated the term "maculo-anesthetic," coined by Hansen and Looft, for the latter form of leprosy.

Regardless of the labels used, however, it is apparent all along the line that two different forms of the disease, not merely two different sites of involvement, were being distinguished. Indeed, the difference is so marked that Bateman,<sup>4</sup> in 1818, discussing *elephantiasis Graecorum* with its

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"tubercles of the face . . . flattened nose, round eyes," wonders if the *leuce Graecorum*, with its "pale colour . . . and its loss of sensibility . . . be not [a] modification of the same disease" We have since learned, of course, that it is

At all events, the clinical classification officially adopted at Manila in 1931<sup>5</sup> divided cases of leprosy into two great groups "neural" and "cutaneous" The quotation marks are intentional, and will be used wherever these words appear in what follows, for the reason that "neural" in the leprologic sense does not always mean neural (i e, neurologic), and "cutaneous" in the leprologic sense does not always mean cutaneous (i e, dermatologic) Nor does the third, minor group in this classification—"mixed" leprosy—mean mixed neurologic and dermatologic disease—for almost every case of leprosy, of whatever type, presents combined neurologic and dermatologic lesions, whereas it is extremely doubtful, as we shall see, whether any case of leprosy ever presents combined "neural" and "cutaneous" involvement in the leprologic sense of those words

*Lepromatous leprosy* ("tubercular" or "cutaneous" leprosy) In 1938, at Cairo, leprologists were sufficiently impressed by the confusion resulting from their special use of the term "cutaneous," to be induced to abandon it, they substituted for it the term "lepromatous"<sup>6</sup> This form of leprosy is characterized by (1) involvement of the skin and mucous membranes and almost invariable involvement of the nerves (as well as of the lymph nodes, bone marrow, spleen, etc), (2) abundance of *Mycobacteria leprae* in the lesions (except in rare recovered cases); and (3) generally rather rapid progression and an unfavorable prognosis The patient regularly fails to react to intradermally injected lepromin

This form of leprosy is indicated by the letter "L" It is important to realize that despite its names, it is capable of producing deformities due to nerve damage, which may be far more conspicuous than the associated skin lesions

*"Neural" leprosy* This form of the disease, the one formerly called "maculo-anesthetic" leprosy, stands in the strongest contradistinction to lepromatous leprosy, and not merely by reason of its moderate predilection for involvement of peripheral nerves "Neural" leprosy is characterized by (probably) invariable involvement of peripheral nerves, and usually of the skin as well, by the presence (except during transitory "tuberculoid reactions") of few or no demonstrable *Mycobacteria leprae* in the lesions, and by a generally slow course and a favorable prognosis The patient regularly reacts strongly to intradermally injected lepromin

This form of leprosy is indicated by the letter "N" Again it is of the greatest importance to realize that despite its name, it can produce skin lesions which may be many times more conspicuous and spectacular than the deformity caused by the associated neurologic lesions

*Mixed leprosy* There has been admitted, for some mysterious reason,

a third clinical group, sometimes set apart from the rest, though officially is merely a subgroup of the lepromatous type "mixed" leprosy, indicated by the initials "LN". It is said to include properly those cases of the lepromatous ("L") type in which neural (i.e., neurologic, as distinct from "neural") changes have supervened. Wade does not seem wholly to approve of this rather remarkable group, since in discussing it, he has referred to the fact that cases of leprosy are "always in a sense 'mixed'". Strictly speaking, since "N" cases are by definition those usually showing few or no bacilli, and "L" cases are by definition those showing many bacilli, persons with "mixed" ("LN") leprosy must be in the peculiar position of having a poor immunologic reaction to *Mycobacterium leprae*, and a strong one, simultaneously. It is as if a patient should have tuberculous sarcoidosis (Besnier-Boeck-Schaumann's disease), and pulmonary tuberculosis with caseation, necrosis, cavitation and positive sputum, at one and the same time.

Altogether, it seems likely that this category of "mixed" leprosy is a hangover from the days when it was called, not "lepromatous-neural" ("LN"), but "cutaneous-neural" ("CN")—in other words, when its name suggested (however erroneously) that it might properly include all lepromatous cases showing fairly obvious evidence of nerve damage. Few leprologists now believe that a patient may have both "neural" and lepromatous types of leprosy simultaneously, although some believe that, rarely, transition may possibly occur from one to the other.

#### VARIETIES OF "NEURAL" LEPROSY

It was thought necessary in 1938, at the Cairo conference, to subdivide "neural" leprosy into three subgroups. This subdivision has been a bone of contention, agreement on it is by no means general, even today. The three official subgroups are (1) anesthetic (indicated by "Na"), (2) simple macular ("Ns"), and (3) tuberculoid ("Nt").

*Purely neural ("anesthetic") leprosy.* The anesthetic subgroup ("Na") includes all "neural" cases characterized by polyneuritic changes only. They regularly show thermal anesthesia (and probably also, if it is looked for, localized anhidrosis), less regularly tactile anesthesia, still less regularly pinprick anesthesia (analgesia), they may also show muscular weakness, paralysis, atrophy or contracture. They do not, by definition, present skin lesions other than purely trophic ones: malum perforans, for example, or atrophy or scaliness, or dermatographism (with no flare about the wheal). Nerve trunks may be thickened and nodulated, and histologically often show (even in their finer cutaneous branches!) typical tuberculoid (sarcoid-like) granulation tissue, with few or no bacilli, the anesthetic skin areas, however, may on the other hand show only banal perivascular inflammatory changes, or none at all.

*Simple macular ("maculo-anesthetic") leprosy.* The "simple macular" subgroup ("Ns") includes those cases presenting the above manifestations

and, in addition to them, hypopigmented (or less often hyperpigmented) macules. These are called "simple macules" by leprologists, because their "macule," unlike the dermatologists' macule, is not necessarily a flat, impalpable lesion, it may be a beefy, indurated, sharply elevated plaque. Like lesions of the preceding subgroup, those of this type may show either banal perivascular round-cell infiltration (usually with a sprinkling of epithelioid cells) or, more often, frank tuberculoid granulomatous architecture. Wade and his associates,<sup>8</sup> Lowe<sup>9</sup> in Calcutta, the Russian leprologist, Stein,<sup>10</sup> and Saunders and Giffen<sup>11</sup> in the Virgin Islands, have shown that tuberculoid architecture can be demonstrated in many "simple macules," and in almost all such lesions when they are erythematous or their borders slightly papular. Ermakova,<sup>12</sup> in Moscow, also found suggestively tuberculoid changes in these lesions, though they were interpreted in the conclusions as banal inflammation.

*Tuberculoid leprosy* The third subgroup, the tuberculoid ("Nt"), consists of those "neural" cases in which the skin lesions are papules, nodules, plaques, or elevated annules, poor or lacking in acid-fast bacilli (except during transitory exacerbations known as "tuberculoid reactions"), and presenting on histologic examination characteristic tuberculoid—sarcoid-like—architecture. These lesions are the "neuroleprides" of Unna, the infiltrated "leprids" of the older leprologists, and the tuberculoid "macules" of modern leprologists—"macules," notwithstanding their being elevated. They are for "neural" leprosy what the leproma or "nodule" is for lepromatous leprosy, the distinctive infiltrated granulomatous cutaneous lesion.

In summary, then, the orthodox clinical classification of leprosy recognizes only two principal varieties: the lepromatous type, with abundant bacilli and a poor prognosis, and the "neural" type, with few bacilli and a good prognosis, the latter type is further subdivided into anesthetic, macular and tuberculoid varieties, on almost exclusively clinical grounds. It is of the utmost importance, for a clear understanding of the disease, to realize that lepromatous leprosy attacks both the skin and the peripheral nerves (as well as other tissues), and that "neural" leprosy *also* attacks both the skin and the peripheral nerves. It is indeed perfectly possible, and by no means rare, to see advanced lepromatous leprosy of nerves with minimal skin involvement, or advanced "neural" leprosy of the skin with minimal nerve involvement. It must be plain from this, that some other and more apt word than "neural" is urgently needed for this group of cases of leprosy.

### THE DERMATOLOGIC CLASSIFICATION

The biologic-dermatologic classification of leprosy was initially propounded by Jadassohn in 1898.<sup>13</sup> He established three categories: the "typical leproma," the "typical (macular) neuroleprid" (without granulomatous changes, at least in the skin), and the "tuberculoid granuloma." These might be briefly designated as "lepromatous," "simple inflammatory,"

and "tuberculoid" Presumably Jadassohn omitted any "simple anesthetic" or purely neural group because he could always classify such cases on a histologic basis as either "simple inflammatory" or "tuberculoid"

As we shall see presently, this "simple inflammatory" group is the most troublesome of all, the criteria for its diagnosis are not well established, they consist rather of a lack of adequate criteria for classification in either of the other two groups We may recall in this connection that much evidence has been adduced by Wade et al,<sup>8</sup> Lowe,<sup>9</sup> Stein,<sup>10</sup> Saunders and Giffen,<sup>11</sup> and perhaps also Ermakova,<sup>12</sup> in support of the view that many cases which might be regarded by some students as "simple inflammation" really belong in the tuberculoid group One is led to wonder whether most "simple inflammatory" cases—which have in common with the tuberculoid group a lack of bacilli, a strong immunologic response, and a good prognosis—may not be in fact tuberculoid cases in which the tuberculoid histologic architecture is simply immature

### THE SOUTH AMERICAN CLASSIFICATION

The Latin American dermatologists have written voluminously on the subject of leprosy in general and its classification in particular We may briefly consider here what two of their principal spokesmen have had to say on the subject

Rabello, Jr,<sup>15</sup> of Brazil, proposed in 1936 a system which, while superficially similar in nomenclature to the orthodox one, actually differed from it fundamentally in spirit He appeared to believe that the dualistic theory was untenable, and that there was no fundamental difference between the macule (or the leprologic "macule"?) and the leproma, either clinically, or in their evolution, or histologically, and that transition from macule to tuberculoid plaque to leproma might occur and frequently did He also believed that tuberculoid and lepromatous lesions might coexist in the same patient, due to local differences in tissue immunity This nihilistic unitarian theory was and still is, of course, quite unacceptable to most leprologists

Pardo-Castello,<sup>16</sup> of Havana, has recently published a much more acceptable classification It begins, unhappily, by dividing the disease into leprosy of skin, leprosy of nerves, and leprosy of other organs—a clinically obvious but misleading and basically meaningless division Each of these is then subdivided into lepromatous, simple inflammatory, and tuberculoid subgroups—the same pattern as that advocated by Jadassohn

He defends the simple inflammatory subgroup on the ground that it is a clinically as well as a histologically indeterminate one, cases of which may subsequently become either lepromatous or tuberculoid It appears however, from our observations and from the work of others, that the transition from bacteriologically negative simple inflammatory lesions to lepromatous ones is rare, whereas the transition from simple inflammatory lesions to tuberculoid lesions is very common Indeed, as previously stated many

cases classified even on histologic grounds as simple inflammatory may be shown by more intensive study (and perhaps a slightly higher index of suspicion) to already present tuberculoid architecture

. Aside from this supposedly indeterminate group, which at all events appears to be only a temporary pigeonhole for any given case, it is thus clear that Pardo-Castello's version of the Latin American classification is essentially the same dualistic one as the current official classification, with the word "tuberculoid" used in place of the word "neural." If the Latin Americans were willing to make their primary division of the disease into "lepromatous" and "tuberculoid" types (even retaining, if they insist, an intermediate indeterminate group), and *then* divide each of these into leprosy of skin, leprosy of nerves, and leprosy of other structures, their view of the disease would be essentially identical with that of the clinical leprologists elsewhere

In the light of recent demonstrations of tuberculoid changes in simple macules, and the comparative rarity of a transition from these to lepromatous leprosy, and in view of the regular demonstration of tuberculoid changes in nerve trunks and branches in cases of purely neural "neural" leprosy, it would seem that the clamor might all be stilled by this simple compromise—merely substitute the word "tuberculoid" for the word "neural" as a designation for all cases of leprosy that manifest scanty bacilli, strong immunologic response, general tendency to more marked involvement of nerves than of skin, slow progression, a good prognosis, and perhaps, in borderline or histologically indeterminate cases, a positive skin reaction to lepromin

### LEPROLOGIC NOMENCLATURE

The terminology of leprosy, as it has developed in the hands of clinicians, chiefly without special dermatologic or histologic training, has become an amazingly confusing affair. A table indicates some of the more confusing special meanings attached by leprologists to certain terms

Word	Dermatologic Meaning	Leprologic Meaning
Neural	Characterized by involvement of nerves	Characterized by scanty bacilli and a good prognosis
Nodule	Circumscribed induration of skin up to about 1 cm. in diameter	Nodule of lepromatous granulation tissue, rich in acid-fast leprosy bacilli
Macule	Circumscribed impalpable alteration of skin color	Circumscribed alteration of skin color, frequently anesthetic, flat or elevated, with few or no acid-fast bacilli in the tissues
Mixed leprosy	Leprosy involving both nerves and skin ( <i>this is erroneous</i> )	Leprosy of combined "neural" and lepromatous types Also widely employed in the (erroneous) dermatologic sense, but only for application to <i>lepromatous</i> leprosy with both nerve and skin involvement

All four of these terms have contributed importantly, by virtue of their highly restricted leprologic meanings, to the current widespread lack of understanding of clinical leprosy. The word "neural," for example, familiar to physicians generally as meaning "pertaining to nerves," has prevented them from going enough further to find out that it means, to leprologists, a relatively benign form of leprosy. The word "macule," similarly, has been taken at its face value by general practitioners talking to leprologists or reading leprosy literature, they have not generally realized that it applies to *any* circumscribed skin lesion, whether flat or elevated, of the relatively benign form of leprosy. "Nodule," in like fashion, has not been fully appreciated as the hallmark of the progressive, relatively communicable form of the disease. And of "mixed leprosy," perhaps the less said the better, for it seems apparent that neither dermatologists nor leprologists really know for certain whether it means lepromatous leprosy of both nerves and skin (and is, therefore, almost exactly as common as lepromatous leprosy itself), or whether it means combined lepromatous and "neural" leprosy of the skin, or of the nerves, or both—and is, therefore, exceedingly rare if not actually nonexistent.

Thus these terms, although they have long and satisfactorily represented to clinical leprologists the existence of two diametrically opposed forms of leprosy, have done precisely the opposite service for the physician whose contact with leprosy is casual and occasional. For him this fundamental distinction has been glossed over, almost as if deliberately. The distinction for him is all "nerve" versus "skin" leprosy, and if a little more intimate acquaintance with the disease teaches him that virtually all cases present *both* nerve and skin involvement, he is apt to feel that his clinical grasp of the disease is reasonably thorough. If he then learns that "neural" leprosy is frequently bacteriologically negative, who can blame him if he thinks he has learned that this is generally true of leprosy involving nerves?

If "cutaneous" was a misleading and confusing name for what is now called "lepromatous" leprosy, then by the selfsame token "neural" is a misleading and confusing term for the other form of the disease. It confuses general practitioners, it confuses dermatologists, and in some connections and in some quarters, at least, it confuses leprologists. It urgently needs to be replaced, and in the light of the studies to which we have referred, the word "tuberculoid" would seem to be the logical term with which to replace it.

### SUMMARY

The orthodox leprologic classification of leprosy divides the disease into "lepromatous" and "neural" forms, with the latter further subdivided into anesthetic, macular and tuberculoid types.

The biologic-dermatologic classification of leprosy divides the disease into lepromatous, macular (simple inflammatory) and tuberculoid forms of

which the latter, and many, if not most, cases of the "macular" type, correspond to the "neural" group of the orthodox leprologists

The South American dermatologists' classification divides the disease basically into lepromatous, nonspecific and tuberculoid forms, there is evidence to suggest that many, if not most, cases of the non-specific type may belong in the tuberculoid group

Current leprologic literature contains four seriously misleading terms "neural leprosy," "macule," "nodule," and "mixed leprosy"

The primary requisites of a new nomenclature and a new classification of leprosy are that they shall represent clearly, and not to the specialist alone, the fact that there are two types of leprosy the one generally strongly bacteriologically positive, the other negative or almost so, the one with a bad prognosis, the other a relatively good one, the one relatively communicable, the other probably only slightly so if at all, the one with a negative cutaneous reaction to lepromin, the other with a positive one, the one histologically a granuloma composed almost wholly of bacillus-laden histiocytes, the other histologically showing aggregates of epithelioid cells and lymphocytes, often in the form of epithelioid tubercles

If the word "neural" be replaced by the word "tuberculoid," the terms "nodule" and "macule" and "mixed leprosy" can then gradually be dropped entirely in their restricted leprologic sense and standard dermatologic nomenclature can generally be permitted to enter into leprologic literature freely, instead of only gradually as at present

### CONCLUSIONS

The present orthodox classification of leprosy is confusing in its detail and misleading in its nomenclature, but it is fundamentally compatible with both the biologic-dermatologic classification and with the South American dermatologists' classification

The three could be reconciled by the adoption of a classification containing two categories lepromatous leprosy and tuberculoid leprosy.

This would promote a much clearer understanding of the fundamental behavior of the disease, and would enormously simplify the classification and evaluation of individual cases

### BIBLIOGRAPHY

1. MORROW, P. A. Leprosy, in A system of genito-urinary diseases, syphilology, and dermatology 1894 Appleton, New York in
2. STELLWAGEN, H. Treatise on diseases of the skin ed 6, 1910, W. B. Saunders, Philadelphia
3. OBERNY, O. S. A practical treatise on diseases of the skin ed 5, 1937, Lea & Febiger, Philadelphia
4. BATESMAN, T. A practical synopsis of cutaneous diseases, ed 5, 1818, Collins & Croft, Philadelphia
5. Report of the Leonard Wood Memorial Conference on Leprosy, Internat. Jr. Leprosy, 1934 p. 329

- 6 Reports of the International Congress of Leprosy Held in Cairo, March, 1938, *Internat. Jr Leprosy*, 1938, vi, 389
- 7 WADE, H W A proposed revision of the Memorial Conference classification of Leprosy, *Am Jr Trop Med*, 1937, xvii, 773
- 8 WADE, H W, and RODRIGUEZ, J N Borderline tuberculoid leprosy, *Internat Jr Leprosy*, 1940, viii, 307  
 WADE, H W, and RODRIGUEZ, J N The skin lesions of neural leprosy II Observations in Cebu, *Internat. Jr Leprosy*, 1937, v, 1-30  
 WADE, H W, and FRASER, N D The skin lesions of neural leprosy III Observations in China, *Internat Jr Leprosy*, 1937, v, 285-308  
 WADE, H W, COCHRANE, R G, and RAJ, M P The skin lesions of neural leprosy IV Observations in Madras, South India, *Internat Jr Leprosy*, 1937, v, 437-462  
 WADE, H W, DE SIMON, D S, and FERNANDO, A C The skin lesions of neural leprosy V Observations in Ceylon, *Internat Jr Leprosy*, 1938, vi, 199-222
- 9 LOWE, J A study of macules in nerve leprosy with particular reference to the "tuberculoid" macule, *Internat. Jr Leprosy*, 1937, v, 181-197
- 10 STEIN, A A Tuberculoid changes in leprosy, *Internat. Jr Leprosy*, 1940, viii, 41
- 11 SAUNDERS, G M, and GIFFEN, H K The skin lesions of neural leprosy in the Virgin Islands of the United States, *Internat Jr Leprosy*, 1942, x, 38
- 12 ERMAKOVA, N The histopathology of simple leprids, *Internat Jr Leprosy*, 1939, vii, 495
- 13 JADASSOHN, J, cited by WADE<sup>14</sup>
- 14 WADE, H W The biological classification of leprous lesions (editorial), *Internat Jr Leprosy*, 1939, vii, 551
- 15 RABELLO, E, JR A clinico-epidemiological classification of the forms of leprosy, *Rev Bras de Leprolog*, 1936, iv, 375, reprinted in *Internat Jr Leprosy*, 1937, v, 343
- 16 PARDO-CASTELLO, V, and TIAAT, F R Leprosy, *Jr Am Med Assoc.*, 1943, cxvi, 1264



# A CURRENT VIEW OF THE RABIES PROBLEM\*

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FOR the past 15 years the number of human cases of rabies in this country has averaged 55 per year. In animals, incomplete data obtained from state departments of health<sup>1</sup> would indicate that for the period 1936-1940, the number is over ten thousand per year. The incidence of the disease in man and lower animals is greatest in the Southern and East-North-Central states, and in California.

Owing to its relatively high incidence in domestic and wild animals as well as to its dreadful clinical reaction, rabies, even though infrequent as a cause of death in man, constitutes an important public health problem.

The first question that comes to mind concerning rabies is: What are the chances of man's contracting rabies following the bite of a rabid animal? This all-important question must remain unanswered. Owing to the universality of the Pasteur treatment there are no modern statistics showing man's susceptibility to this malady. The older calculations are unreliable, extremely variable, and of little value. Thus, mortality following bite by a presumably rabid dog is stated as ranging from 2-50 per cent or even higher.<sup>2</sup> We know, however, that there are certain circumstances which will affect the rate of mortality among individuals who seek antirabies treatment. The location of the bite, for example, is very important. Bites on the head and neck result in the highest rate, followed by bites in the upper extremities, lower extremities, and trunk. Among other factors which strongly influence the outcome are the species of animal inflicting the bite, the number and depth of the wounds, the interposition of clothing, and the age of the individual.

It will be well to mention at this point that of persons who are given antirabies treatment following a bite by a rabid or suspect animal, about 90 per cent report bites by dogs, 5 per cent by cats, and the remainder by cattle, horses and other species.

Three aspects of the rabies problem are of immediate practical interest namely, diagnosis, prevention, and complications following treatment.

*Diagnosis* Diagnosis of rabies in human patients is not a difficult clinical problem. The characteristic symptomatology plus evidence of a recent animal bite does generally permit an accurate diagnosis. Death follows in all cases. The problem of diagnosis in dogs or other animals is complicated. The clinician sees it in the following way: A person has been bitten by a dog, is the dog rabid? The answer to this question is important since it will

\* Read at the Meeting of the American College of Physicians, New York, October 20, 1944.

<sup>1</sup> From the Laboratories of the Rockefeller Institute for Medical Research, New York.

decide whether antirabies treatment has to be applied or not. Since, as we shall see later, complications may follow the treatment, one should not give it unless reasonably indicated. The observation of the dog may give to an expert veterinarian a fairly accurate answer. In general, however, it will be necessary to observe the animal for eight or 10 days before one can be certain. If the dog survives, rabies is excluded, whereas if death ensues the probability is that the dog was rabid.

However, it is for the laboratory to decide whether or not the animal had rabies. No methods at present available are satisfactory because they depend on the death or sacrifice of the animal. Serological reactions which would permit a diagnosis during life of the animal have not been developed. The methods at present in use are (1) histological examination of the brain of the animal, and (2) inoculation of cerebral tissue from the suspect into laboratory animals.

Animals infected with rabies virus exhibit in their brains typical microscopic lesions, particularly, the large pyramidal cells of Ammon's horn show Negri inclusion bodies. Negri bodies have special characteristics so that their identification is simple. They are always found in the cytoplasm, have a typical inner structure and special staining properties. Their presence establishes the diagnosis.

The other method for the diagnosis of rabies consists in the inoculation of a suspension of brain tissue from the suspect animal into other animals. All mammals are more or less susceptible to an intracerebral inoculation of rabies virus, but the animal of choice is the mouse.<sup>3</sup> Special strains of albino mice are highly susceptible to rabies and uniform in their response. The method of diagnosis consists in inoculating five or six mice intracerebrally with a suspension of brain tissue. In positive cases these mice will show signs of central nervous system involvement within seven to ten days and die usually within the next 24 hours. The brains of these mice exhibit Negri bodies. Of these two methods the latter is more accurate than the former. In a recent survey obtained by the Georgia State Board of Health, of 771 animal brains found positive for rabies on mouse inoculation, 81 or 10 per cent were negative for Negri bodies.<sup>4</sup> On the other hand all suspect animals that had Negri bodies on inoculation into mice yielded rabies virus.

*Prevention* Preventive measures against rabies infection are (a) general, which aim at the eradication of rabies at its source, with the purpose of destroying rabies reservoirs and preventing the spread of rabies from animal to animal or animal to man, (b) individual, which have as their goal the prevention of the disease in man after exposure.

Since dogs are the main source of rabies in this country general measures for the control of the disease should be directed toward them. They are within the functions of public health officials. Muzzling of dogs, destruction of stray animals and strict quarantine are the three main steps. Such procedures have proved their efficacy on several occasions. Thus, a country

like Australia has been kept free of rabies because of the enforcement of quarantine laws. In England relaxation of the ordinances on muzzling and leashing has been found to result in a sharp increase in the number of cases of rabies.

Prevention of rabies in dogs by means of vaccination has been advocated as a method of diminishing the general incidence of the disease. In order to evaluate the efficacy of canine antirabies vaccination we depend on two kinds of data, those deriving from field observation and those from experiment. Field data are usually difficult to appraise properly, though incidence of rabies among dogs apparently diminishes following large-scale vaccination, no critical analysis of the results is available at this time.

What is recorded in the literature up to 1938 on animal experiments, as surveyed by Webster,<sup>5</sup> offers very little to support the claim of the efficacy of antirabies vaccination. In recent years, however, new methods have been developed for the study of the potency of rabies vaccines with the result that we have nowadays not only more effective vaccines but also more precise means of determining their value.

By means of the mouse test it has been possible to study the variables which influence the potency of vaccines. Their elimination has served, therefore, to improve the antigenicity of the latter. The strain of rabies virus used in the preparation of the vaccine, the animal species in which the vaccine is propagated, the age of the animals employed, the nature of the agent used for the inactivation of the virus, the length of time during which the vaccine is usable, are all important factors.

Vaccines for dogs consist of emulsions of rabies infected brain tissue in physiological salt solution in concentration of either 20 or 33 per cent. These suspensions are inactivated by adding some chemicals, usually phenol or chloroform. Such vaccines cannot contain any active virus according to regulations of the United States Bureau of Animal Industry. The dose is usually 5 c.c. per dog.

The efficacy of vaccines for use in dogs can be determined in the laboratory by the mouse test. This consists essentially in vaccinating mice with the test material, then infecting them, along with untreated controls, with a range of dilutions of fixed rabies virus. The challenge dose is given intracerebrally and by comparing the titer of the virus in the vaccinated and control mice one has an index of the potency of the vaccine.

Results of experiments in dogs in this laboratory indicate that 5 c.c. of vaccine per dog may not be sufficient to protect against heavy infection. It is probably true that the experimental is a more severe test than the natural infection so that this amount of vaccine may be sufficient in most cases. It would be advisable to give a second dose of 5 c.c. in order to establish a more solid immunity. How long immunity following vaccination lasts in dogs has not been determined. It is our experience that the potency of rabies vaccines as prepared for market has improved considerably in the past few years. Vaccines for use in man can be similarly tested.

In man vaccine is given following exposure, as a preventive treatment. The incubation period of rabies in man is, on the average, 30 to 60 days. Since the effective immunity following vaccination is established in a shorter time, the usual procedure in persons exposed to a rabid animal consists in starting vaccination as soon as possible after exposure.

There are different types of vaccines for human use, some of which contain active virus, others of which contain only inactivated virus. The original Pasteur vaccine is employed at present only in very few places. This method consists in the use of desiccated rabbit cords infected with rabies virus. Beginning with a cord dried for 14 days containing no active virus, successive injections are given in the next 13 days with cords that are dried for fewer and fewer days progressively until the last injection which contains fully active material.

At present inactivated virus is used as vaccine in man. Such vaccines consist generally of a 4 per cent brain suspension inactivated by different chemicals. One of the vaccines most commonly used in this country and abroad is the Semple vaccine in which phenol in concentration of 0.5 per cent is employed as inactivating agent, in other vaccines formalin, ether, or chloroform is added or heat is used. Fourteen injections of 2 c.c. each are usually given. In special cases both the number of injections and the amount of vaccine are increased.

A great deal of material has been accumulated in the past 15 years regarding the effect of vaccination in human beings. McKendrick has collected statistics from most Pasteur Institutes throughout the world and analyzed them very carefully. In his latest review<sup>6</sup> over 1,000,000 cases of human antirabies treatment were analyzed. A number of interesting facts were revealed. The mortality among those people who were given the treatment was 0.33 per cent, this low figure cannot be taken as a real index of the value of rabies vaccination because the degree of exposure among people varied markedly. Of the four categories of treated individuals the greatest number fall in the groups in which exposure to rabies has not been proved or is doubtful. Another startling fact which emerges from McKendrick's analysis is that no vaccine surpassed others tested, with the possible exception of a slight apparent superiority of one containing active virus, although even in this instance the statistical analysis gives no conclusive proof. Moreover, the promptness with which antirabies treatment was begun did not influence the outcome, indeed, contrary to general belief McKendrick revealed that in a group of 581,519 Europeans, those whose treatment was begun immediately to four days after exposure showed a higher mortality rate than those treated later. In fact when immunization was delayed eight to 14 days the chances of survival were greater. Among 321,348 non-Europeans, no disadvantage was apparent in delaying treatment up to 14 days after exposure.

Nevertheless, in spite of these rather puzzling data treatment should be recommended in all cases of proved or suspected exposure to rabies. Owing

to the low mortality rate found in people who have had the Pasteur treatment as well as to the low incidence of complications following rabies treatment, this is the most logical procedure

*Complications* Complications of different types are unusual following antirabies treatment. For the most part they are mild, consisting of local reactions at the site of inoculation, with erythema, edema, pain, pruritus and tenderness. The side reactions are of minor consequence, and should not stop treatment.

More severe reactions may follow, such as peripheral neuritis and dorso-lumbar myelitis. The latter may arise gradually with fever and weakness, recovery is the usual outcome. Treatment should be discontinued in the presence of such signs.

Finally the most severe complications are the paralytic accidents, often of a Landry type, with high fever, headache, nausea, vomiting, urinary retention and ascending paralysis of lower extremities. Paralysis may continue to ascend involving the bulbar nuclei. Recovery may occur in the milder cases and sometimes permanent disability is a sequel. Death follows in about one-third of these cases. In McKendrick's analytical review there are listed 181 paralytic accidents in a series of 1,060,832 treatments (one in 5861), of those 48 were fatal (one in 22,100). It must be pointed out here that paralytic accidents are more frequent following use of vaccines containing active than inactivated virus. Thus McKendrick shows that paralytic accidents developed in one person of 3398 after treatment with attenuated virus (cords), one of 3194 after treatment with diluted virus, whereas the incidence was one of 8,887 following phenol-inactivated vaccine and one of 17,620 following heat-killed vaccines.

Since any definite superiority of one vaccine over others has not as yet been demonstrated, a vaccine should be selected on the basis of minimal possible post vaccinal complications, those containing only inactivated virus should, therefore, be chosen.

#### BIBLIOGRAPHY

- 1 WEBSTER, L. T. Rabies, 1942, The Macmillan Company, New York.
- 2 KOCH, J. Lyssa. In KOHL, W., and VON WASSERMANN, A. Handbuch der pathogenen Mikroorganismen, Jena, G. Fischer, 3rd edition (edited by KOHL, W., KRAUS, R., and UFFENHUTH, P.), 1929, VIII, 547-694.
- 3 WEBSTER, L. T., and DAWSON, J. R., JR. Early diagnosis of rabies by mouse inoculation. Measurement of humoral immunity to rabies by mouse protection test, Proc Soc Exper Biol and Med, 1935, XXXII, 570-573.
- 4 JOHNSON, H. N. Rabies. Oxford Loose-leaf Medicine, 1943, Oxford University Press, New York.
- 5 WEBSTER, L. T. The immunizing potency of antirabies vaccines. A critical review, Am Jr Hyg, 1939, XXX (Sec B), 113-134.
- 6 MCKENDRICK, A. G. A ninth analytical review of reports from Pasteur Institutes on the results of anti-rabies treatment, Bull of the Health Organization of the League of Nations, 1940, IX, 31-78.

# CASE REPORTS

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## MALARIA COMPLICATED BY PNEUMONIA; TREATMENT WITH SULFADIAZINE AND ATABRINE\*

By Z TAYLOR BERCOVITZ, F A C P, Lt COL, M C, A U S

THE purpose of this paper is to report the case of a patient suffering with *P falciparum* malaria complicated by pneumonia and successfully treated with both atabrine and sulfadiazine. The clinical picture of the onset of pneumonia confused the picture by suggesting a relapse of the malaria. The diagnosis was cleared up by physical examination.

### CASE REPORT

E D S, a white male, 53 years old, was brought to the attention of the writer because during what was presumably a relapse of malaria he failed to respond to the administration of quinine. The patient was an engineer who two weeks after his return from Africa, where he had gone 10 weeks before, complained of feeling tired. He had had a chill, his temperature rose to 103°-104° F for two to three days, and he had watery stools. Blood smears for malarial parasites were positive, and the diagnosis of *P falciparum* malaria was made. The patient was given quinine, 30 gr daily for about four days. The temperature fell to about 100° F at the end of that time, and the quinine dosage was reduced to 10 gr a day.

Within a day or two the temperature began to rise again and the patient began to have a dry cough. He complained of pain in the lower left axilla. It was at this time that the writer was called in for consultation. Examination of blood smears confirmed the diagnosis of *P falciparum* malaria made by the attending physician. On physical examination signs of lobar pneumonia were discovered over the left lower lobe. The quinine was discontinued, and a dose of 0.3 gm atabrine was given immediately. Sulfadiazine therapy was instituted also, 20 gm immediately and then 10 gm every four hours thereafter, day and night, a total of 12 gm having been given before the patient was admitted to a hospital on April 5, 1942, 10 days after the onset of his malarial symptoms.

On admission the patient was acutely ill and delirious. There seemed to be no apparent benefit from the sulfadiazine therapy. Roentgen-ray on April 6 confirmed the diagnosis of lobar pneumonia of the left lower lobe.

Sputum examination showed type 7 pneumococcus. The blood level of sulfadiazine on April 6 after the administration of a total of 12 gm of the drug, was 129 mg per 100 cc. Sulfadiazine, 1 gm every four hours, day and night, was continued, and 200,000 units of type 7 antipneumococcic rabbit serum were given intravenously. The patient was also started on atabrine 0.1 gm daily.

Repeated examinations of the urine were negative. Blood cultures taken on several days were negative. The percentage of hemoglobin varied from 54 to 72. The red blood cell count ranged from 2,900,000 to 3,940,000 per cubic millimeter. The white blood cell count on admission was 5,750 per cubic millimeter and subsequently

\* Received for publication February 10, 1944.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

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#### BIBLIOGRAPHY

1. WINTER, L. T.: Rabies, 1942. The Macmillan Company, New York.
2. KOPPEL, J.; LANGE, H.; KÖHLER, W. and VON WASSERMAN, A.: Handbuch der pathogenen Mikroorganismen, Jena, G. Fischer, 3rd edition (edited by KÖHLER, W., KRAUS, R. and UHLENHUTH, P.), 1929, viii, 347-404.
3. WINTER, L. T. and DAWSON, J. R. JR.: Early diagnosis of rabies by mouse inoculation. Measurement of humoral immunity to rabies by mouse protection test. *Proc. Soc. Exper. Biol. and Med.*, 1935, **xxvi**, 574-575.
4. JOHNSON, H. N.: Rabies. Oxford Lectures in Medicine, 1943, Oxford University Press, New York.
5. WINTER, L. T.: The increasing potency of antirabies vaccines. A critical review, *Am. J. Hyg.*, 1939, **xxx** (Sec. B), 112-134.
6. MCKENDRICK, A. G.: A critical analytical review of reports from Pasteur Institutes on the results of antirabies treatment. *Bull. of the Health Organization of the League of Nations*, 1940, **ix**, 31-78.

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THE purpose of this paper is to report the case of a patient suffering with *P falciparum* malaria complicated by pneumonia and successfully treated with both atabrine and sulfadiazine. The clinical picture of the onset of pneumonia confused the picture by suggesting a relapse of the malaria. The diagnosis was cleared up by physical examination.

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On admission the patient was acutely ill and delirious. There seemed to be no apparent benefit from the sulfadiazine therapy. Roentgen-ray on April 6 confirmed the diagnosis of lobar pneumonia of the left lower lobe.

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From the Department of Medicine, New York Post-Graduate Medical School and Hospital.



the count fluctuated between 4,100 and 7,000 per cubic millimeter. The differential count showed 43 to 77 per cent polymorphonuclear neutrophils, 18 to 53 per cent lymphocytes, and 1 to 9 per cent monocytes. On several days, myelocytes, metamyelocytes, polymorphonuclear eosinophiles and basophiles were evident. In view of the low hemoglobin and blood elements, the patient received three blood transfusions of 500 c.c. each on April 6, 9, and 16. He was also given ferrous sulphate and liver extract during his illness.

In all, the patient received a total of 59.5 gm. sulfadiazine over a period of 12 days. The sulfadiazine was discontinued on April 14. During the period of administration the sulfadiazine level of the blood ranged from 4.3 mg. per 100 c.c. on the day the drug was discontinued to 13.4 mg. per 100 c.c. on the fifth day of administration. The atabrine, in a dosage of 0.1 gm. daily, was given for 22 days, and discontinued on April 27. On April 22 the patient was started on anayodin, three tablets (0.25 gm. in each), three times a day, which was continued until May 4.

Blood smears for malarial parasites were negative on April 8 and thereafter. The temperature fell to normal the day after admission, and then rose to 101.4° F. the next day and remained over 100° F. for three days. It then fell to normal where it remained until April 26, when it rose to 102.4° F. This rise was attributed to the occurrence of obliterative pleurisy at the left base.

Inquiry into the patient's past history revealed that he had had an attack of left sided pleurisy in 1917, and then in 1924 during a severe cold or grippe roentgen-ray showed "a spot on the lung" on the left side, which was still present on roentgen-ray later.

The patient was discharged on May 13, 1942 free from malarial and pneumonic symptoms. Roentgenogram still showed slight productive changes at the left base and elevated left diaphragm with partial obscuration of the left costophrenic sinus, suggesting old, pleuritic thickening at the left base.

When he was discharged from the hospital he was given atabrine tablets (0.1 gm. in each), with instructions to take one daily for the following 60 days. This plan was faithfully carried out, the patient having been seen at the office at weekly intervals for almost one year. During that time no relapses of malaria occurred. In the interim the patient made another trip to a malarial country in the tropics. While on that trip and for 60 days subsequently he took one tablet of atabrine (0.1 gm.) daily. Repeated thick film examinations of blood were negative for malaria.

## DISCUSSION

It is evident from the facts that the onset of the pneumonia was at first considered a relapse of the malaria. It was only because the patient failed to respond to quinine that the writer was consulted. Careful physical examination revealed the presence of lobar pneumonia of the left lower lobe and ruled out the malarial relapse. This emphasizes the need for careful physical examination during malaria and watchfulness for the occurrence of other diseases which may obscure the diagnosis.

It is significant that the atabrine therapy, although continued for 22 days in a daily dosage of 0.1 gm., did not interfere with the therapeutic efficacy of sulfadiazine in the pneumonia, nor did the latter conflict with the value of the atabrine in controlling the malaria. Following the initial course of treatment with atabrine, the patient was given a daily dosage of 0.1 gm. for 60 days, and subsequent to this when on a trip to a tropical country he took atabrine daily while on the trip and for 60 days thereafter. Under this régime, there was no relapse of the malaria, and the blood continued to be free of malarial parasites on repeated

monthly examinations after discontinuing the atabrine. When discharged from the hospital the patient was able to carry on his duties as an engineer.

It is interesting to note, with reference to the therapeutic compatibility of atabrine and sulfadiazine, the experience of Harned and Cole.<sup>1</sup> These investigators observed that quinine administered orally with sulfapyridine to rats increased the total amount of sulfapyridine absorbed and the amount excreted in the urine in the form of conjugated crystalline acetylsulfapyridine. Consequently, the authors concluded

"In view of the close similarity between the conjugation and excretion of sulfapyridine in man and the rat it appears that treatment in the human of a double infection for which quinine and sulfapyridine would be simultaneously used should be managed by other drugs until it is established that the quantities of these drugs employed in human therapy do not increase the hazard of urolithiasis."

However, when atabrine, which in the treatment of malaria is used in approximately one-tenth of the weight employed for the salts of quinine, was substituted for quinine in these rat experiments, the excretion of sulfapyridine was not affected.

Sulfathiazole was used simultaneously with atabrine without any untoward effects in a case of *P. falciparum* malaria with concurrent right lower lobe pneumonia which the Standard Oil Company<sup>2</sup> was good enough to bring to the attention of the writer. This patient was treated at the Caripito Hospital of the Standard Oil Company in Venezuela, and was the only case reported in response to a request by the Standard Oil Company that its South American physicians report any cases in which pneumonia and malaria existed simultaneously in the same patient treated with one of the sulfonamides and at the same time with atabrine or plasmochin. This patient received 0.1 gm atabrine three times daily for seven days, a total of 2.1 gm, followed by 0.01 gm plasmochin three times daily for the subsequent three days, and then 5.0 gr quinine sulfate three times daily for a week. During this time, a period of 17 days, the patient received a total of 55 gm of sulfathiazole. This case progressed satisfactorily to a rapid recovery, without complications due to the medication he received.

The results obtained in this case and in the case described by the writer suggest that in man sulfadiazine or sulfathiazole may be used in conjunction with atabrine for the treatment of pneumonia during a malarial attack.

#### SUMMARY AND CONCLUSIONS

1. A case of malaria complicated by pneumonia is described.
2. Atabrine therapy of the malaria did not in any way influence the effect of sulfadiazine on the pneumonia in the case reported by the author.
3. The daily administration of 0.1 gm atabrine for 22 days while under treatment for the pneumonia and for 60 days on two occasions subsequently, did not adversely affect the patient.
4. The experience in the author's case suggests that atabrine may be used safely simultaneously with sulfadiazine.
5. Reference is made to a similar case treated with atabrine and sulfathiazole with no untoward effects.

## BIBLIOGRAPHY

1. HARNED, B. K., and COLL, V. V. A therapeutic incompatibility between sulfapyridine and quinine, Jr Pharmacol and Exper Therap, 1942, LXXIV, 12-51.
2. Personal communication from the Standard Oil Company

## "METASTATIC" CALCIFICATION IN SOFT TISSUES OF LEGS IN OSTEITIS DEFORMANS; CASE REPORT \*

By BERNARD SELIGMAN, M.D., F.A.C.P., and LOUIS NATHANSON, M.D.,  
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Soft tissue, "metastatic" calcification has been reported in only one previous case of osteitis deformans, which was described by Wells and Holley.<sup>1</sup> Metastatic calcification is to be distinguished from calcinosis. The former represents calcification of apparently healthy tissue due to changes in the composition of the blood calcium and phosphorus salts, phosphatase, or alkalinity. The latter represents another stage of an underlying pathologic process of certain tissue such as occurs in scleroderma, sclerodactyly, Raynaud's disease, dermatomyositis, progressive lipid dystrophy, myositis ossificans, etc.<sup>2</sup>

In a 59 year old man who had Paget's disease for six to seven years and had received 10 minims of ergosterol, activated 10,000 times, daily for 15 days, Wells and Holley found at autopsy extensive metastatic calcification of the lungs, of the kidneys, of the gastric mucosa, of focal areas in the skin, of the endocardium of the left atrium, extensive calcification of the anterior leaflet of the mitral valve and of the cusps of the aortic valve. No gross evidence of renal insufficiency was noted. Microscopically the skin showed heavy focal calcium deposits in the subcutaneous tissue surrounded by a fibroblastic reaction with many young fibroblasts and foreign body giant cells.

In the individual herein described extensive calcium deposits were seen radiographically in the soft tissues of both legs as well as in the larger blood vessels of the torso, and numerous negative centered faceted stones were identified on roentgen-ray examination of the gall-bladder. This patient had received small doses of viosterol and calcium over a period of one and one half years. She had evidence of decompensated arteriosclerotic heart disease with edema of the legs of eight years' duration.

### CASE REPORT

E. M. was known to have had Paget's disease for six years in November 1935, when she was under the care of Dr. Leo Mayer at the Hospital for Joint Diseases. Two months previously she had stepped off a trolley car and felt pain in the region of her left hip and groin. Roentgenograms taken at this time were not available to us. These areas were not tender but were painful on weight bearing. She had been almost entirely confined to bed following this accident. The pain was relieved after a rest of four weeks in bed. She was also given 10 grains of calcium lactate, five minims of viosterol three times a day and received ultraviolet irradiation of the entire body for 21 days.

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From the Jewish Sanitarium and Chronic Hospital, Brooklyn, New York

- Her grandmother had Paget's disease. One of her sisters was a diabetic. The patient had had diphtheria at the age of 17 and had suffered from many sore throats over a period of years. She was married in 1916 and had two children in 1921 and 1924, both of whom were delivered by Cæsarean section. With the second a hysterectomy was performed and a large fibroid removed. After the latter she developed postpartum fever and a phlebitis of both lower extremities.

Before admission to the hospital she complained of dyspnea on exertion and orthopnea, and had nocturia as well as edema of the ankles. Her blood pressure was elevated to 170 mm Hg systolic and 110 mm diastolic. She had systolic murmurs at the apex and base of the heart. She had pulsations over the entire precordium. The legs showed a pitting edema. These persisted for the rest of her life.

She was seen by one of us (BS) February 12, 1936 at the age of 57. For several months she had complained of constipation, belching, heartburn, and epigastric distress when she walked after eating. This was more evident after she became stouter. She had frequency of urination and would get up two to three times a night to urinate. For one month she had a headache. She had been deaf for three years. She complained of stiffness, was drowsy, and fell asleep easily.



FIG 1 Roentgenogram of skull

She was keen in her responses, mild and soft spoken. The head was carried forward with the chin resting on her chest. It was symmetrical and markedly enlarged, with the broad end up. The face was triangular in outline. The temporal arteries were markedly tortuous and prominent. The vision was so poor in her left eye that she could not count fingers. She had bilateral nerve deafness, the ear drums were dull, thickened and gray, and all the landmarks were obliterated. Her hearing was markedly impaired, more so on the right side, and only a loud voice from the left side was audible. Her teeth were carious and many were missing. The right supratonsillar area was scarred. The veins in the neck were distended. The chest was markedly enlarged. The breasts were enormous in size. The heart was markedly enlarged and she had a pulsation of the entire precordium. A systolic murmur was

heard over the aortic and mitral areas. The abdomen was markedly obese and flaccid. Two scars of the previous operations were noted. The back was squat and crushed in on itself. She had pitting edema of both legs. She had moderate bowing of both tibiae. No limitation of motion of the hip joint was found. She was not tender over the left hip or groin, but stated that these areas were still painful on weight bearing. She had marked sclerosis of the vessels of the wrist. No clubbing nor cyanosis of the fingers was noted. Her blood pressure was 160 mm Hg systolic and 70 mm diastolic to 150 mm Hg systolic and 100 mm diastolic. She was placed on a restricted diet and lost 12 pounds, from 219 to 207.

She continued to take 7 minims of viosterol and 40 grams of calcium lactate daily for a period of one and one half years. She received in all 3,957,120 I U of vitamin D. The only complaint which could be attributed to the calcium deposits, found later

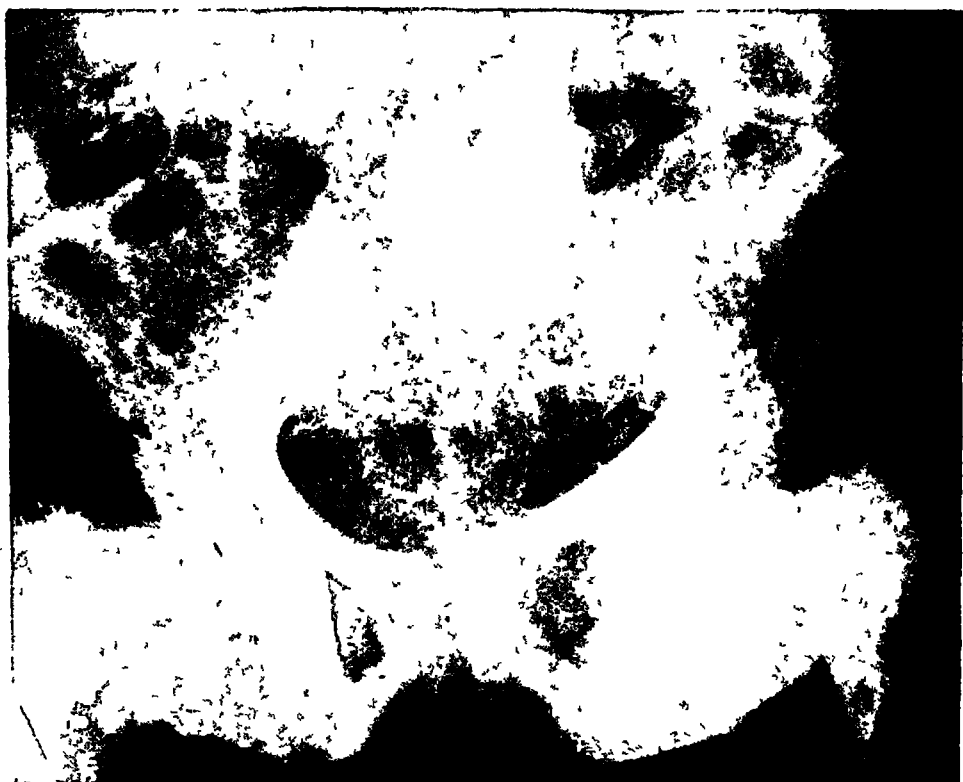


FIG 2 Roentgenogram of pelvic bones, gall-stones and calcification of aorta

on roentgenographic examination of the legs, was a tenseness of the skin, however, her legs were edematous. In March 1939, she was admitted to the Coney Island Hospital because she developed a bronchopneumonia, type three pneumococcus was found in the sputum. While walking around during her convalescence, she slipped and fell, fracturing her left femur. At this time Dr. Emanuel Mendelson was able to observe on roentgen examination numerous areas of calcification in the subcutaneous tissues of the leg particularly posteriorly. On July 1, when the fracture healed and she was able to get about on crutches, she was transferred to the Kings County Hospital. Later she became bedridden and was admitted to the Jewish Sanitarium and Chronic Hospital on August 28, 1939. She used two pillows when she slept, was constipated, had non-bleeding piles, frequency and urgency of urination and incontinence for one year.



and facial bones resembled those in leontiasis ossium. The maxillary, ethmoidal and sphenoidal sinuses were obliterated by the overgrowth of bone. The bones of the base of the skull were dense and eburnated. The same alterations were present in the temporal bones. In addition to the advanced distortion of the pelvis due to Paget's disease there was a flattening and deformity of the hips producing a coxa vara configuration.



FIG 3 Roentgenogram of right leg showing calcium deposits in soft tissue

The examination of the lower extremities showed evidence of Paget's disease of the bone, but in addition showed extensive calcification of a granular and mottled type within the soft tissues. This was most marked in the subcutaneous tissue and extended through the muscle planes particularly along the mesial and posterior surfaces of the lower extremity from below the level of the knee to above the ankle joint. The calcification was somewhat more marked in the 1942 examinations than in those made in 1939. No soft tissue calcification was present in the upper extremities.

Moderately advanced calcification was present in the abdominal and pelvic vessels, but no calcification in the popliteal or tibial vessels at the level where the soft tissue calcification was found. Several fractures of both lower extremities were present which healed normally. The soft tissue calcification was apparently not related to the fractures in so far as we could determine. Numerous negative centered faceted gall-stones were present in the gall-bladder. Minimal calcification was present in the thoracic aorta and mottled changes could be demonstrated through both lungs,



FIG 4 Roentgenogram of left leg showing calcium deposits in soft tissue

many of which had a circumscribed appearance suggesting calcification within pulmonary vessels. We were, however, by no means certain of this. The heart was tremendously enlarged in all its diameters during the entire period of her observation.

An electrocardiographic tracing on March 10, 1942 showed ventricular premature contractions, left axis deviation with slurring of QRS<sub>2</sub>. On December 30, 1942 fibrillation was present and all the QRS complexes were of low voltage. The chest findings remained the same until April 14, 1943 when a patch of pneumonia developed at the left base.



The final diagnosis was Paget's disease, arteriosclerotic heart disease associated with hypertension, cardiac failure and auricular fibrillation, cerebral and coronary thromboses with a terminal bronchopneumonia. She had, as accompanying features, bilateral nerve deafness, gall-stones and calcification of the soft tissues of the legs.



FIG 5 Chest roentgenogram showing enlargement of heart and calcium deposits in lung fields

### DISCUSSION

In Paget's disease, tissues other than bone have been found to contain calcium deposits. Renal calculi are not uncommon, occurring in 10 per cent of Snapper's cases.<sup>3</sup> Then again, renal calculi are not infrequently found in bone lesions of many different etiologies.<sup>4</sup> Moehlig and Adler,<sup>5</sup> in a series of 26 cases of Paget's disease, found gall-stones in three of them. They found calcified adenomata of the thyroid gland in two patients and calcified fibroids in three of the 12 women in their series.

In the case of Wells and Holley,<sup>1</sup> besides the "metastatic" soft tissue calcification, supersaturation of the blood with calcium produced when carbon dioxide was lost through respiration caused calcium precipitation in the venous pulmonary circulation of the alveoli, the pulmonary arteries escaped but the small veins were heavily calcified. Often about the acid secreting glands of the stomach was found a dense ring of calcium deposition when the excretion of hydrochloric acid had left a compensatory degree of local alkalinity. In the kidney, where secretion of acid urine had also produced local alkalinity, there was a heavy microscopic deposit of calcium in the tubules and to a lesser degree in the arteries.

Our patient in 1935-1936 was given calcium and viosterol, an accepted form of therapy at that time. Roentgenograms taken just previous to this are unavailable to us and we are unable to state definitely whether calcification of the soft tissues existed at that time, but it was not so reported by a competent roentgenologist. When examined three years later, she showed extensive calcium deposits in both legs. These increased in amount from 1939 to her death in 1943. During the entire period of observation she had cardiac insufficiency with marked edema of both legs and feet. The veins of both lower extremities had been affected by phlebitis 11 years previously.

It is difficult to explain with the information at hand why calcification of the soft tissues of the body occurred in this case and in that described by Wells and Holley. In *ostëitis deformans* a negative calcium and phosphorus balance is present in the earlier and more active form of the disease and a positive balance occurs in the later and less active stages with the blood calcium and phosphorus levels normal throughout.<sup>6</sup> The serum phosphatase, however, is markedly increased during the entire disease and sometimes so to extremely high levels.<sup>7</sup> When present, hypercalcemia (in an individual with skull signs of Paget's disease) means that we may be dealing with a coexisting hyperparathyroidism.<sup>8</sup> Albright<sup>9</sup> feels that the condition starts as a destruction of the bone which fits in with the findings of a negative calcium and phosphorus balance present earlier in the disease, osteoblastic stimulation due to increased stress and strain is the second step and results in overgrowth of bone and increase of serum phosphatase. In our patient, the phosphatase level was high in 1935.

London and Bernheim<sup>10</sup> administered 10 c c of 20 per cent calcium gluconate intravenously in 17 cases with unidentified stages of Paget's disease and found a lack of the normal expected elevation of the blood calcium. An increased affinity of the bones and other tissues for this calcium was their explanation. Moehlig and Adler<sup>5</sup> were unable to prove that feeding calcium phosphorus compounds or large doses of vitamin D improved the osteoporosis. On the contrary they feel that the giving of calcium is distinctly harmful as there is a tendency to increase calcium deposits in the soft tissue, then, too, viosterol may increase the arteriosclerosis which is so frequently present in Paget's disease. Vitamin D feeding had no appreciable effect on the calcium phosphorus balance in two cases described by Albright et al. In one of Sugarbaker's cases 10 years of treatment with vitamin D and calcium showed indifferent changes.

We want to stress, in these two cases, the absence of chronic renal insufficiency which can be associated with the protracted presence of calcium and phosphorus ions in the blood in concentrations far in excess of those at which deposition of calcium phosphate may be expected theoretically.<sup>11</sup> In the case of Wells and Holley the kidneys showed no gross evidence of renal damage at autopsy. In our case the blood phosphorus level was reported as elevated in 1939 but later that year it became normal. This would disprove any permanent renal damage. We are in no position to state whether or not renal or pulmonary calculi existed.

In our case edema and venous stasis due to heart failure were observed in both lower extremities for eight years. It should be noted that after her last Cesarean section in 1924 she had a bilateral phlebitis. In an attempt to explain disseminated ossification of the lungs, Wells and Dunlap<sup>12</sup> claim that venous

stasis or general circulatory impairment favors bone production provided that other conditions conducive to ossification are present. Furthermore, they feel that in occasional cases a rise in  $\text{CO}_2$  is responsible for an increase of calcium in the blood. Since the calcium deposits were not universal but were limited to the legs, we feel that the edema played an important role in its causation.

The therapy of Paget's disease is as obscure as is the etiology of the condition. However, Snapper still advocates the administration of calcium, phosphorus and ultraviolet rays in certain cases with osteomalacia. "The condition of the bone improves although the underlying osteitis deformans remains the same." In calcinosis, a ketogenic diet and disodium phosphate have been advised as well as a unilateral thyroidectomy and parathyroidectomy.<sup>14</sup> The latter has been carried out in osteitis deformans<sup>14</sup> but is not generally employed. Gill and Stein<sup>15</sup> suggest a low calcium and phosphorus diet supplemented with magnesium carbonate. The relation of protein, sex hormones,<sup>16</sup> and adrenal cortex<sup>17</sup> to bone metabolism has been stressed. Mochlig and Adler have found in Paget's disease a glucose tolerance curve which resembled that of a diabetic; they gave 15 units of insulin together with a constant weighed diet and found a disappearance of bone and head pains with an increase of strength.

No effective measures for the treatment of Paget's disease have yet been devised. However, certain facts have been established. Microscopically in this disease there is a tendency to the precipitation of calcium salts in the tissues.<sup>18</sup> The markedly increased phosphatase may have a close causal relation to the calcification.<sup>19</sup> Feeding of calcium phosphate or vitamin D may also promote the precipitation of calcium salts. The minerals and vitamin D used in our case, however, we believe were probably incidental rather than important factors in causing the deposition of calcium salts in the legs. It is interesting to note that the calcium deposits acted like foreign bodies, as evidenced by the granulomatous reaction in the case of Wells and Holley.

### SUMMARY

A second case of gross calcification of the soft tissue of the extremities occurring in Paget's disease is described. This was present in both legs which were edematous from cardiac failure. In a previous case of soft tissue and visceral calcium deposition the patient received viosterol. The calcium deposits acted as a foreign body in causing a granulomatous reaction. In our case, the patient received viosterol and calcium. We feel, however, that the giving of calcium and viosterol was only a coincidence in our case but see no indication for its use in the later stages of osteitis deformans. These cases emphasize the finding of calcium deposits in the later stages of Paget's disease when a positive calcium balance exists.

### BIBLIOGRAPHY

- 1 WELLS, H. G., and HOLLEY, S. W. Metastatic ossification in osteitis deformans, (Paget's disease of bone), *Arch. Path.*, 1942, xxxiv, 435.
- 2 ROTHSTEIN, J. L., and WELT, S. Three cases of calcinosis universalis and calcinosis circumscripta in infancy and in childhood, review of literature, *Am. Jr. Dis. Child.*, 1936, lii, 368.
- 3 SNAPPER, I. Medical clinics on bone diseases, *Interscience*, 1943, p. 142.

- 4 Editorial Urinary calculi in bone diseases, Jr Am Med Assoc, 1936, cvi, 469
- 5 MOEHLIG, R C, and ADLER, S Carbohydrate metabolism disturbance in osteoporosis and Paget's disease, associated soft tissue disturbances and results of various therapeutic procedures, Surg, Gynec, and Obst, 1937, lxxv, 747
- 6 SUGARBAKER, E D Osteitis deformans (Paget's disease of bones), review of 51 cases, Am Jr Surg, 1940, xlviii, 414
- 7 BODANSKY, M, and BODANSKY, O Biochemistry of disease, 1940, Macmillan Co, New York, p 411
- 8 ALBRIGHT, F, AUB, J C, and BAUER, W Hyperparathyroidism a common and polymorphic condition as illustrated by 17 proved cases from one clinic, Jr Am Med Assoc, 1934, cxii, 1277
- 9 ALBRIGHT, F, SMITH, P H, and RICHARDSON, A M Postmenopausal osteoporosis Its clinical features, Jr Am Med Assoc, 1941, cxvi, 2473
- 10 LONDON, I M, and BERNHEIM, A R Calcium tolerance curves in Paget's disease of bone, Jr Lab and Clin Med, 1937, xxiii, 18
- 11 JAFFEE, H L, and BODANSKY, A Serum calcium clinical and biochemical considerations, Jr Mt Sinai Hosp, 1943, ix, 901
- 12 WELLS, H G, and DUNLAP, C E Disseminated ossification of lungs, Arch Path, 1943, xxxv, 420
- 13 NUNEZ, B E, and ARTHUR, P S Calcinosis report of 2 cases, Med Ann District of Columbia, 1943, xii, 301
- 14 BALIN, M Parathyroidism, Ann Surg, 1932, xcvi, 649
- 15 GILL, A B, and STEIN, I Bone metabolism its principles and relation to orthopedic surgery, Jr Bone and Jt Surg, 1936, xviii, 941
- 16 GARDNER, W U, and PFEIFFER, C A Influence of estrogens and androgens on the skeletal system, Physiol Rev, 1943, xxiii, 139
- 17 BERMAN, L Studies of Paget's disease, effect of adrenal cortical extract treatment upon blood phosphatase in Paget's disease, Endocrinology, 1936, xx, 226
- 18 MARINE, D Personal communication
- 19 GOMORI, G Calcification and phosphatase, Am Jr Path, 1943, xlv, 197

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## PULMONARY ACTINOMYCOSIS DUE TO *ACTINOMYCES GRAMINIS*\*

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THE term, actinomycosis, is now applied by Topley and Wilson<sup>8</sup> to two groups of diseases of man and animals in which Actinomyces-like organisms are encountered. In the first group, the proliferation of an anaerobic organism as *Actinomyces bovis* gives the appearance of colonies which have a ray structure in pus or tissues and often are described as "sulphur granules" or *Druzen*. In the second group are included all aerobic filamentous branching organisms which form a felted mycelium without any radial arrangement and without granule formation. Two type species are *Actinomyces graminis* which is non-acid-fast and forms no granules in tissues, and *Actinomyces asteroides*, which is acid-fast and forms no granules in tissues.

Of human actinomycosis, in 60 per cent lesions occur in the face and neck.

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in 20 per cent in the abdominal cavity, 15 per cent in the thorax, leaving 5 per cent involving the skin and other portions of the body.<sup>4</sup> The mortality of pulmonary actinomycosis varies from 70 per cent<sup>2</sup> to 95 per cent.<sup>4</sup> The mode of transmission is obscure in infections with both the aerobic and anaerobic Actinomyces. Schneider and Finucane<sup>6</sup> believe the organism enters the body through a cavity in a tooth or through an open wound. Diagnosis is best made by microscopical and cultural examinations of the affected tissues. Prophylactic measures should be taken against the discharge from all lesions. No satisfactory methods of treatment can be recommended.

Interest in the presence in tissue of the aerobic, non-acid-fast Actinomyces, *Actinomyces grammis*, has been stimulated during the past decade, although it had been isolated from cases of human actinomycosis in 1891 by Bostroem.<sup>7</sup> In 1934 Biggart<sup>1</sup> reported the finding of *Actinomyces grammis* in a fatal case of generalized actinomycosis in a woman with the primary abscess in the left lung and secondary involvement of both lungs and liver, spleen, kidneys, and subcutaneous tissue of the left thigh and right arm. Zeitlin and Lichenstein<sup>8</sup> in 1937 described a case of actinomycotic abscess of the brain secondary to a small focus in the lung from which an aerobic Actinomyces was cultivated, although they failed to state whether or not this organism possessed acid-fast properties. Holt<sup>5</sup> in 1941 cultivated *Actinomyces grammis* from the pus of a brain abscess in the left parietal lobe of a woman 36 days prior to death. Permission for an autopsy was not granted and it could not be ascertained whether the lesion was primary or secondary. A low grade pathogenicity of this Actinomyces was demonstrated for rabbits and pathologic lesions similar to those in man were produced.

The pertinent clinical, bacteriological and pathological data of a case of pulmonary actinomycosis is presented in which *Actinomyces grammis* (Bostroem) was identified in bronchial secretion, sputa, and pleural fluid before death, and in pleural fluid and multiple abscesses of the lung on postmortem examination.

#### CASE REPORT

J. E. F.,\* a 16 year old high school boy, was quite well until September 22, 1943, when he was taken with pain in the left chest anteriorly, headache, general malaise, temperature of 102° F, and a nonproductive cough. There was stiffness of his joints but no swelling or tenderness.

He was first seen by me (J. P. L.) and admitted to St. Luke's Hospital on October 29, 1943, when he volunteered the following additional information. He had had night sweats during the preceding week, and dyspnea and precordial pain. His mother had noticed nervousness and poor color since the onset. There were no other systemic symptoms of significance, except a weight loss of 30 pounds.

Past history revealed he had measles, mumps, varicella, and pertussis in childhood. There was no history of pneumonia or asthma, or surgical operation. The family history was negative except that his mother had had a thyroidectomy before his birth. There was no family history of tuberculosis. He was a native of Virginia, lived in the suburbs of Richmond, and was active in athletics, having frequently played football in open fields.

Physical examination revealed the following significant findings. Height 5 feet, 9½ inches, weight 128½ pounds, temperature 101.7° F, and pulse 108. He was a

\* We wish to acknowledge our indebtedness to Dr. M. J. Page who referred this case.

well developed, but poorly nourished boy who had a notable pallor. His sinuses transilluminated poorly and there was a postnasal mucoid discharge. The cervical, axillary and inguinal glands were not enlarged. There was an area of dullness on percussion at the left base posteriorly extending for two or three inches above the level of the diaphragm, and an area of cardiac dullness extending 12.5 cm to the left of the mid-sternal line. No râles were heard, but the breath sounds in these areas were diminished or absent. The heart sounds were of fairly good quality. There was a soft systolic murmur in the pulmonic area. The blood pressure was 100 mm Hg systolic and 60 mm diastolic. The liver and spleen were not palpable. The genitalia, reflexes, and extremities were normal.

Examination of the chest two days later revealed dullness at the left lung apex anteriorly extending down the whole anterior surface of the left chest.

Laboratory examinations on admission were as follows: Blood Hemoglobin 67 per cent (Sahli), white cell count, 15,400, with 85 per cent neutrophils, 12 per cent lymphocytes, 1 per cent mononuclears, and 2 per cent eosinophils. Urine Amber, cloudy, specific gravity 1.026, acid, faint trace of albumin, no sugar and no acetone. rare red blood cell, one to two pus cells per high power field, large amounts of mucus, and many crystals (sulfadiazine). Sputum Bloody with numerous Gram positive filaments, but no acid fast bacilli or filaments. Agglutination tests with antigens of *E. typhosus* ('O' and 'H' antigens), *B. paratyphosus*, *Proteus* X 19, *Br. abortus*, *P. tularensis* were all negative. Six blood cultures were negative. An electrocardiogram was normal in all four leads.

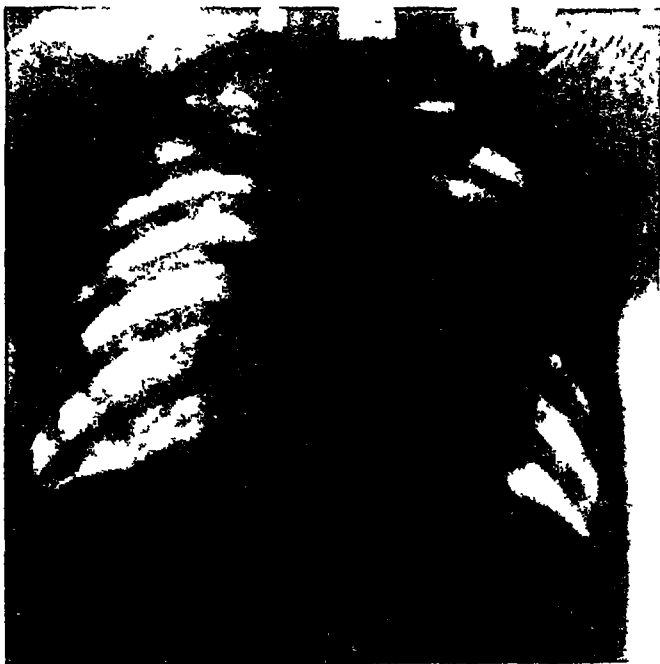


FIG 1 Flat plate of chest made October 29, 1943

On October 29, Dr. J. L. Tabb of the McGuire Clinic made a roentgenogram of his chest and reported that "appearances indicate an atypical pneumonia extending outward from the root of the left lung practically to the periphery (figure 1).

Prior to admission to the hospital, a total of 15 grams of sulfadiazine over a 10 day period was administered. On November 3 he was given 2 grams sulfadiazine 2 grams four hours later, and then one gram every eight hours for five days and

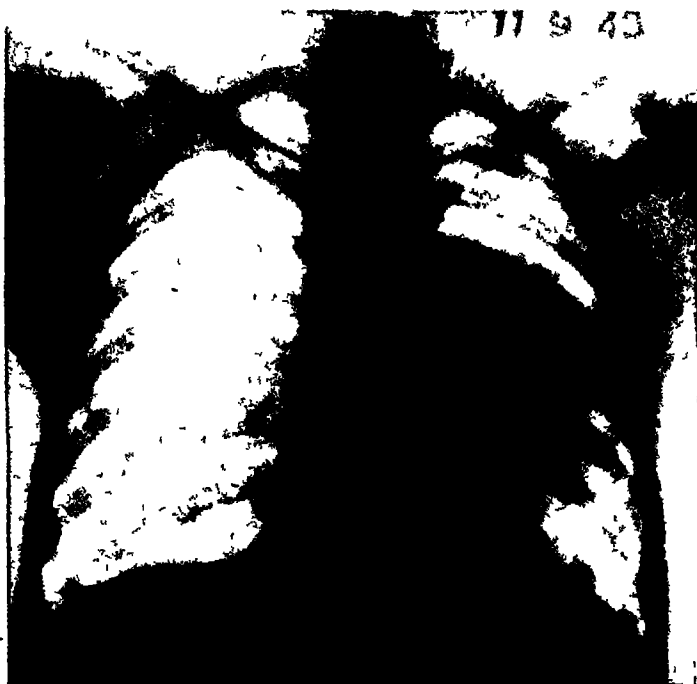


FIG 2 Flat plate of chest made November 9, 1943

night. There was no appreciable effect on the temperature which averaged  $101^{\circ}\text{F}$ .

Chest roentgenogram on November 9 showed a spread of the pneumonic process in the left lung and three rarefied areas resembling cavities were noted in this process (figure 2).

On November 10, Dr. Porter Vinson of the Medical College of Virginia, made a bronchoscopic examination of the patient. An inflammatory lesion causing partial obstruction of the left upper lobe bronchus was reported. Material obtained during bronchoscopy revealed the presence of numerous Gram positive filaments resembling morphologically actinomyces (figure 3) and many yeast-like organisms resembling



FIG 3 Smear preparation of *Actinomyces grammis* in bronchial secretion. Gram's stain ( $\times 1440$ )

monilia No acid fast bacilli or filaments were demonstrated on direct microscopic examinations. Cultures were not made on this specimen. On three subsequent specimens of sputa, *Actinomyces graminis* was identified by cultural means, although *Monilia albicans* was found in only one of these specimens. Studies of *Actinomyces graminis* isolated from sputum were also made after intravenous and intraperitoneal inoculations into white mice. Within two weeks after injections, the mice were either sacrificed or died. Actinomyces were seen in the multiple abscesses formed in the liver, spleen, lung and kidneys, when studied in direct smears and in sections stained by Gram's method. No "sulphur granules" or Drusen were formed in the tissues. The characteristic picture seen was the presence of irregularly stained, Gram positive, branching filaments in granulomatous tissue with multiple abscess formation and necrosis. At no time were acid fast filaments or bacilli found.

*Actinomyces graminis* as isolated from this case possessed the following characteristics: **Morphology** Irregularly staining branching filaments (figure 3). No terminal granules. **Trinctorial properties** Gram positive. Non-acid-fast in young and old cultures and in tissue, sputum and pleural fluids. **Motility** Non-motile. **Biological properties** Grew readily on ordinary culture media and on media for fungi at room temperature and at 37° C in 24 to 48 hours. Aerobe. Failed to grow anaerobically in chopped meat and Brewer's media.

**Semi-solid dextrose brain infusion agar** Abundant surface growth in 24-48 hours at 37° C. Early growth was white and feathery. It gradually deepened in color from cream to orange to brown and became more firm and adherent. Surface growth might show definite colony formation or it might be a dull, finely granular or mealy pellicle.

**Blood agar** Aerobically within 24 hours at 37° C, definite chalky white, feathery surface colonies developed which varied in size from pin point to pin head. Colonies increased in size in 48 to 72 hours. Appearance changed as center changed from cream to yellow to brown and became more granular. Periphery increased its feathery or rhizoid arrangement. Generally firm and adherent to solid media. Difficult to emulsify.

**Corn meal agar and Sabouraud's dextrose agar** Growth at 20° C essentially the same as that on blood agar at 37° C.

**Dextrose broth** Early colony formation resembled balls of cotton (figure 4) on surface of broth. Older growths deepened in color. Failed to ferment dextrose.

**Loeffler's blood serum** No liquefaction. Typical colony growth. White feathery periphery with cream to orange to brown centers.

**Gelatin** No liquefaction. Abundant typical surface growth. Growth decreased along stab.

**Milk** Slightly alkaline. Typical surface growth.

**Chopped meat** No growth.

**Brewer's medium** Aerobic growth abundant. No anaerobic growth.

**Carbohydrate semi-solid infusion agar** No fermentation during four weeks of dextrose, lactose, saccharose, maltose, mannite, xylose, dulcitol, dextrin, sorbitol, levulose, arabinose, or inositol. Surface growth abundant. Colonies showed cream-orange pigmented centers with effuse white feathery edges. Adherent to media.

Beginning November 13 the patient received daily roentgen-ray therapy totalling 800 r to the left anterior chest and 400 r to the posterior aspect (220 KV with thoracic filter used). Twenty-four hours after the first roentgen-ray treatment the temperature rose from a level of 101° to 103° F. In addition to the radiation, he was given 15 grains of sodium iodide by vein daily and saturated solution potassium



iodide 21 drops three times daily, increasing by one drop three times daily until his discharge from the hospital when he was receiving 35 drops three times a day. On November 26, he received 500 c.c. blood by vacuum flask citrated method without reaction.

His course at home was progressively downward. He suffered drenching sweats, increasing dyspnea with a respiratory rate of 36 per minute and a wracking cough. His appetite gradually failed and he became too weak to sit up. On December 11 a loud pericardial friction rub was heard. A punctate maculopapular rash appeared over his abdomen and legs, which was thought to be an iodide skin reaction. He was getting 50 drops saturated solution potassium iodide three times daily, and the drug was temporarily discontinued. Intradermal injections of both *Mompha albicans* and *Actinomyces grammis*, isolated from the sputum, produced little or no cutaneous reaction 48 hours later.



FIG. 4 Surface colony of *Actinomyces grammis* in dextrose broth after aerobic cultivation for 72 hours at 37° C (× 12)

The antigens used for the skin testing were a suspension of the growth of 72 hour cultures in physiological normal salt solution, standardized to MacFarland's nephelometer No. 3 and autoclaved for 15 minutes at 15 pounds pressure. Liquid phenol was added in 0.5 per cent concentration. An attempt to immunize the patient with a vaccine was not thought advisable.

On December 16 he was readmitted to St. Luke's Hospital. His temperature was 101° F, pulse 160, and respirations 32. His eyes had a glassy appearance. The entire left chest was flat on percussion both anteriorly and posteriorly. Moist râles were heard throughout. The pericardial rub had disappeared, but the heart tones were of poor quality. Blood pressure was 90 mm Hg systolic and 70 mm diastolic. There was moderate abdominal distention. The hemoglobin was 64 per cent (Sahli), the white count 44,900 cells per cubic millimeter with 93 per cent neutrophils and 7 per cent lymphocytes. The total count on the day of death was 70,000 cells per cubic millimeter with 91 per cent neutrophils. The urine was acid and showed a faint trace of albumin, but was otherwise negative.

The electrocardiogram showed ST elevation in the three standard leads, consistent with changes noted in acute pericarditis. The roentgenogram showed complete homogeneous opacity of the left lung and bronchial thickening of the right.

On December 17, 500 c.c. of cloudy, straw colored fluid were removed from the left pleural cavity. A culture of this fluid showed the presence of *Actinomyces graminis*. Neither acid fast bacilli or filaments nor monilia could be demonstrated.

During the last 48 hours of his illness, he received 100,000 units of penicillin with no apparent benefit and died quietly December 17.

**Autopsy** Actinomycosis of the left upper lobe of the lung with invasion of the pericardium, subacute adhesive pericarditis, chronic myocarditis (figure 5), and left empyema as well as an acute splenic tumor and chronic passive congestion of the liver were reported by Dr. J. H. Scherer. Sections of the lung stained with hematoxylin and eosin showed chronic granulation tissue with multiple foci of abscess formation and necrosis. Bacteriological stains of the sections of the lung and pericardium with



FIG 5 Lung-heart gross specimen showing multiple actinomycotic abscesses (at right) with direct extension into pericardium

Gram-Weigert stain revealed numbers of the branching actinomycetes (figure 6). The presence of *Actinomyces graminis* in the pleural fluid collected at the time of autopsy was again demonstrated by cultural means, although no monilia were found. Cultures of the abdominal fluid taken at autopsy proved negative for both actinomycetes and monilia. No acid-fast bacilli or filaments were seen in direct smears of the sediments of either the pleural or abdominal fluids collected after death.

#### SUMMARY

1 An actinomycosis infection, probably primary in the lung, of a previously healthy 16 year old boy is reported.

2 Treatment with sulfadiazine, sulfamerazine, roentgen-ray radiation, iodides and blood transfusion was ineffectual.

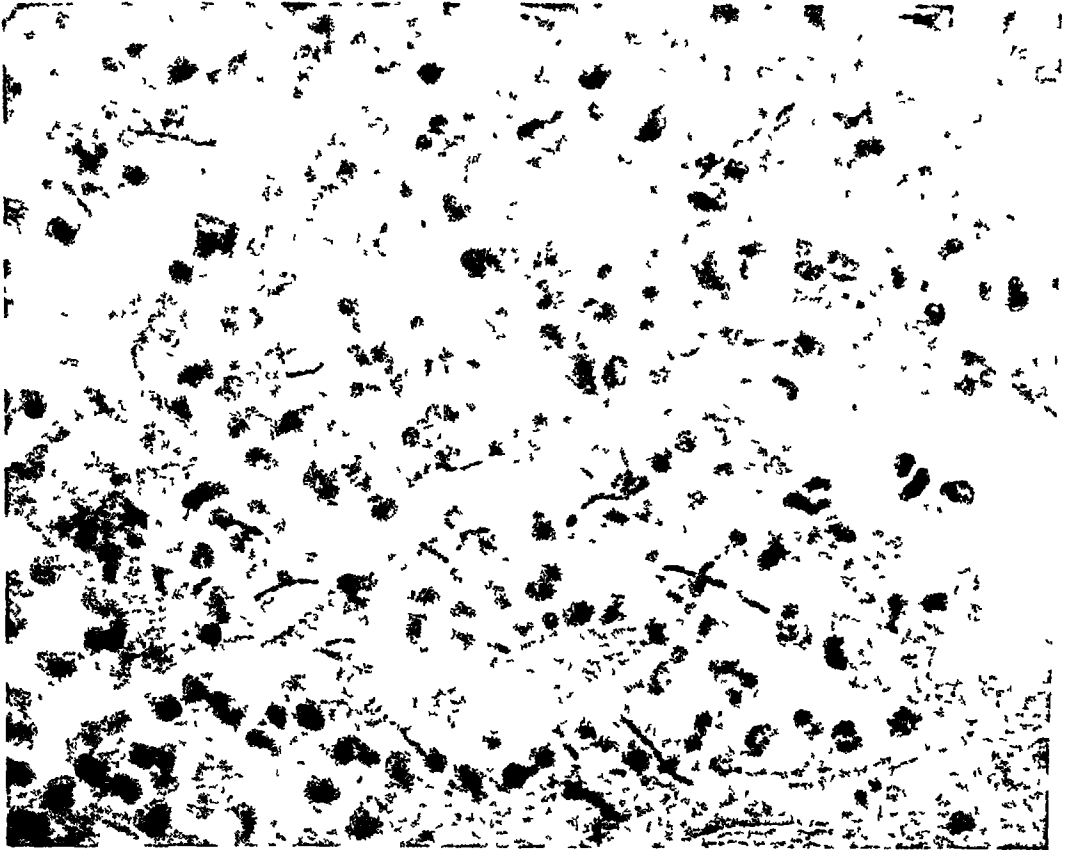


FIG 6 Section of human lung showing branching filaments of *Actinomyces graminis* distributed throughout the chronic granulation tissue without any radial arrangement and without any formation of granules or *Drusen* Gram-Weigert stain ( $\times 720$ )

3 From the onset of symptoms to death, the duration was 85 days

4 *Actinomyces graminis* was identified by bacteriological means in the bronchial secretion, sputa and pleural fluid prior to death and in pleural fluid after death

5 Postmortem gross studies revealed actinomycosis of the left upper lobe of the lung with direct extension into the pericardium giving rise to a subacute adhesive pericarditis, chronic myocarditis, and empyema on the left side. Gram positive branching filaments of *Actinomyces graminis* were distributed throughout the tissue. No radial arrangement or granule formation (*Drusen*) was observed.

6 A low grade pathogenicity for white mice was shown by the *Actinomyces graminis* isolated. Bacteriological and pathological findings were the same as seen in the studies of man.

#### BIBLIOGRAPHY

- 1 BIGGART, J. H. Actinomycosis graminis, Bull. Johns Hopkins Hosp., 1934, liv, 165-173
- 2 BOLLINGER, O. Ueber eine neue Pilzkrankheit beim Rinde, Centralbl. f. d. med. Wissensch., 1877, xv, 481
- 3 BOSTROEM, E. Untersuchungen ueber die Aktinomykose des Menschen, Beitr. z. path. Anat. u. z. allg. Path., 1891, ix, 1

- 4 CUTLER, E C, and GROSS, R E Actinomycosis of the lung and pleura, *Am Rev Tuberc* 1940, xli, 358-367
- 5 HOLT, REBECCA A Unreported case
- 6 SCHNEIDER, L V, and FINUCANE, D L Pulmonary actinomycosis complicated by pneumothorax treatment, *Dis Chest*, 1941, vii, 229-235
- 7 SMITH, R T Actinomycosis of liver and lungs, *Am Jr Surg*, 1943, lx, 438-442
- 8 TOPLEY, W W C, and WILSON, G S The principles of bacteriology and immunity, 2nd Ed, 1936, Wm Wood & Co, Baltimore, Chap LIV, Actinomycosis, actinobacillosis, and related diseases, pp 989-999
- 9 ZEITLIN, H., and LICHENSTEIN, B W Actinomycotic abscess of brain, *Arch Path*, 1937, xxviii, 58-66

## MECHANISM OF REFLEX ANURIA \*

By GEORGE A WOLF, JR, M D, *New York, N Y*

ALTHOUGH in urologic literature a syndrome of so-called reflex anuria has been recognized, its explanation has never been satisfactory Kasten,<sup>1</sup> in classifying the anurias, includes an inhibitory form of reflex anuria said to be the result of a fall in blood pressure below the critical level necessary for glomerular filtration He states that such anurias may accompany a fall in renal blood pressure following splanchnic stimulation in abdominal operations Another more common cause of reflex anuria is said to be the decreased glomerular filtration pressure resulting from a fall in systemic blood pressure associated with shock from painful injuries or prostrating illnesses Moon,<sup>2</sup> however, points out that a fall in systemic blood pressure is not a constant accompaniment of renal shut down and cites instances following crush injuries in which diminished renal output persisted after the blood pressure had returned to normal To explain such occurrences a noxious substance produced by the damaged tissues of patients with crush injuries has been postulated as a factor concerned in the diminution of renal function

Hipsley<sup>3</sup> came to the conclusion that all of the cases of reflex anuria which he could discover in one hospital might be explained on the basis of calculous obstruction of the urinary tract which had not been clinically evident at the time the diagnosis of reflex anuria was made Elward<sup>4</sup> has reported a case in which transient unilateral suppression of renal function was unassociated with shock, with changes in blood pressure, or with organic obstruction to the urinary tract Adler<sup>5</sup> has described a patient in whom anuria appeared to be related to emotional factors and was relieved by hypnosis

Study of the following case casts some light upon mechanisms which may be involved in reflex anuria

### CASE REPORT

The patient was a 32 year old male who considered himself well until approximately one year before his entry into the hospital, at which time he began to suffer from headaches Two weeks before admission the patient noted the onset of gross

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From the Department of Medicine, Cornell University Medical College and New York Hospital, New York City

hematuria and occasional sharp right flank pain which persisted until the time of admission. He was found to have a blood pressure of 230 mm Hg systolic and 108 mm diastolic. The urinary output for the eight hours prior to cystoscopy was 600 c.c. Cystoscopy was performed without local or general anesthesia. Grossly bloody urine was observed coming from the right ureter and no phenolsulfonphthalein was excreted from either kidney in 10 minutes. Bilateral retrograde studies were completed and found to be normal. The patient did not void following cystoscopy until the next day when, in spite of a 3000 c.c. intake, only 100 c.c. of bloody urine were excreted. The blood pressure was 160 mm Hg systolic and 110 mm diastolic. Fifty per cent glucose and theocalcin were given repeatedly. The urinary output averaged 200 c.c. a day in spite of an intake of over 2000 c.c. a day for five days. The patient was seen eight days after cystoscopy by a consultant who made the following observations. The temperature was 38.2° C, the pulse was 100 per minute, the respirations were Cheyne Stokes in type, and the blood pressure was 170 mm Hg systolic and 100 mm diastolic. The patient was in a semidelirious state. The eye grounds revealed evidence of arteriolar disease with hemorrhage and exudate. The mucous membranes were dry and the breath was urinous. The lungs were found on auscultation to contain many moist râles at both bases. The heart was enlarged to the left and the rate was rapid but regular. There was a loud to and fro precordial friction rub. The venous pressure was estimated to be 200 mm of water. The liver was just palpable, and there was no edema.

The urine examination showed a specific gravity of 1.012, two plus albumin, many red blood cells but no casts. There was a moderate anemia and a leukocytosis of 40,000. The blood urea nitrogen had risen from 57 to 193 milligrams per cent. The carbon dioxide combining power was 34 volumes per cent. The serum proteins were 6.1 grams per cent. The serum phosphorus was 10.4 milligrams per cent and the serum calcium was 9.3 milligrams per cent. Intravenous injection of phenolsulfonphthalein resulted in the excretion of no detectable dye in two hours. At this time the patient was no longer anuric but was excreting an average of 1000 c.c. of urine a day. During the following week his condition became progressively worse and resulted in his death from uremia on the fifteenth day following cystoscopy. Postmortem examination of the kidneys revealed a diffuse pyelonephritis with multiple small abscesses throughout both kidneys. The renal arterioles showed rather marked thickening and hyalinization of the medial coat. The tubules showed blockage by leukocytes and precipitated protein. The glomeruli were unremarkable.

### DISCUSSION

Wolf<sup>6</sup> has shown that in normal individuals the application of a painful stimulus to the head by means of a pressure device may result in suppression of urine flow. By means of diodrast and inulin clearances this effect could be attributed specifically to a decrease in renal blood flow which was not associated with a fall in systemic blood pressure. The blood pressure rose during the application of the painful stimulus even though the subject developed cold, moist extremities and became pale and nauseated. It was further shown that the decrease in the rate of glomerular filtration was relatively small when contrasted with the diminution in renal blood flow. Although it was pointed out that the response of the kidneys to pain resembled that seen following the injection of adrenalin (Chasis, et al<sup>7</sup>), it was not postulated that the change in renal blood flow was an adrenalin effect. Rydin and Verney<sup>8</sup> have demonstrated that in dogs the oliguria associated with a "startle" reaction is not dependent upon the innervation of the kidneys or the presence of the adrenal glands. They postulate

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- 7 CHASIS, H, RANGEL, H A, GOLDING, W., and SMITH, H W The control of renal blood flow and glomerular filtration in normal man, *Jr. Clin Invest.*, 1938, **xvii**, 683-697.
- 8 RYDIN, H, and VIRNIA, E B The inhibition of a water diuresis by emotional stress and by muscular exercise, *Quart Jr Exper Physiol*, 1938, **xviii**, 343-374
- 9 CORCORAN, A C, and PAGE, I H Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs, *Jr Exper Med*, 1943, **lxviii**, 205-224
10. DUFF, G L, and MORR, R H Bilateral cortical necrosis of the kidneys, *Am Jr Med Sci*, 1941, **cc**, 428-450.

## DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY CHRONIC RHEUMATIC AORTIC AND MITRAL ENDOCARDITIS\*

By GEORGE W PARSON, M D, F A C P, *Tevarkana, Arkansas-Texas*

CONGENITAL dextrocardia with situs inversus is a relatively uncommon anomaly. LeWald<sup>1</sup> recorded an incidence of one in 35,000 physical examinations of recruits for the United States Army. We have recognized two in approximately 15,000 private patients. Dextrocardia complicated by acquired organic heart disease must be rare. No careful search of the literature has been made but a recent paper,<sup>2</sup> in which a case of dextrocardia complicated by calcareous aortic stenosis<sup>3</sup> was described, listed only five former case reports. In these the acquired lesions were mitral stenosis,<sup>3</sup> hypertensive heart disease,<sup>4</sup> coronary thrombosis,<sup>5</sup> hypertensive and coronary heart disease,<sup>6</sup> and syphilitic aortitis and aortic insufficiency.<sup>7</sup> A patient with dextrocardia and coronary artery disease was reported by Crawford<sup>8</sup> in 1939. In the same year, Konar<sup>9</sup> described a case of congestive cardiac failure due to emphysema in a patient with generalized transposition of viscera. Autopsy findings were given, but no electrocardiographic data were presented. Apparently no case of dextrocardia complicated by combined aortic and mitral endocarditis has been recorded. The following report should be of interest.

### CASE REPORT

Mrs I A C, a 24 year old white housewife, was referred to us September 14, 1942 because of heart disease. Dextrocardia had been recognized at the age of one month. Infancy, childhood, and young adult life had been perfectly normal. The usual activities, including basketball, caused no abnormal symptoms. In December, 1939 at the age of 21 years, the patient had an acute illness characterized by fever and red, swollen, painful joints. She recovered in five weeks without any known cardiac complications. The patient was married at the age of 18 years and had two children, three and one-half years and 14 months old. The first pregnancy was uneventful. During the second a cardiac lesion was recognized, but apparently no myocardial failure developed. In September, 1941, approximately two months postpartum the patient was put to bed with sore throat, fever and dyspnea. She improved, but influenza necessitated bed rest again late in 1941 and she was not well after that. Although she was out of bed from time to time, dyspnea was always troublesome. A few weeks before our examination the ankles were swollen and they were sore enough to interfere with walking, and five weeks prior to our studies, she was hospitalized.

\* Received for publication February 18, 1944

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pitting edema, but the tissues over the sacrum and hips were puffy. Physical examination was otherwise not remarkable.

A specimen of urine was negative except for an occasional pus and red blood cell. The leukocyte count was 12,100. The blood count was otherwise normal. Blood urea was 20 mg per 100 cc of blood and the blood Kahn reaction was negative. The sedimentation rate was not determined.

Fluoroscopic and roentgenologic examination of the chest (figures 1 and 2) re-



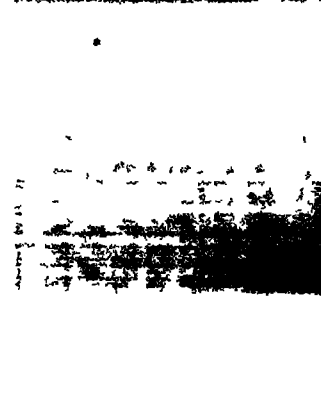
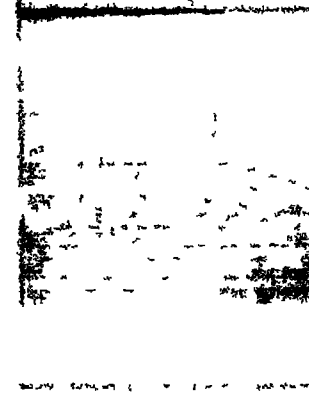
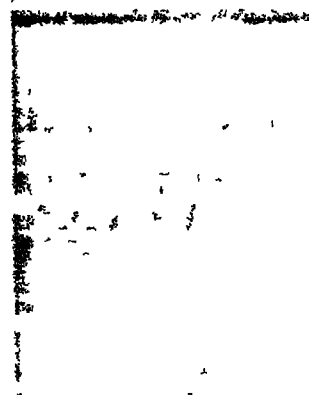
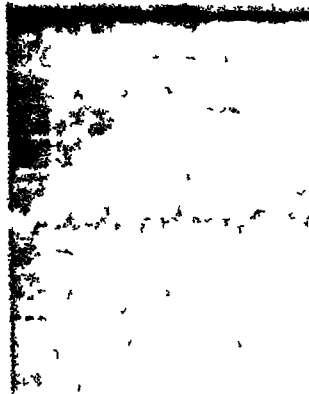
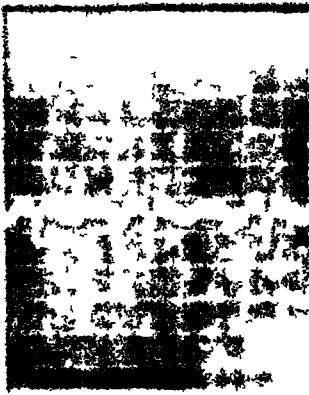
FIG 2 Left Anterior Oblique View Displacement dorsally of barium filled esophagus by enlarged left auricle (black arrow)

vealed in the anterior view transposition of the heart, moderate cardiac enlargement, small right-sided aortic knob, marked enlargement of the conus (black arrow) of the right ventricle, increased markings in the lung fields and enlarged hilar shadows. The left leaf of the diaphragm was higher than the right. In the left oblique view the important finding was dorsal displacement of the barium filled esophagus by an enlarged left auricle (black arrow, figure 2).

Transposition of the stomach and colon was demonstrated by fluoroscopic and roentgenographic examination following a barium meal.

Electrocardiographic examination\* (figure 3a) Sinus rhythm, ventricular rate

\* These tracings were made October 25, 1942. Those taken September 14, 1942 were not satisfactory for reproduction.



92, right axis deviation, P-R interval 0.22 second and QRS interval 0.08 second. Lead I revealed the characteristic features of congenital dextrocardia, i.e., inversion of P-, QRS- and T-waves, and in addition broad (0.13 sec) notched P-waves. In Lead II (transposed Lead III) there were small (3 mm) S-waves, normal P-waves, and inverted T-waves. Lead III (transposed Lead II) showed upright, broad (0.12 sec), notched P-waves, small (2 mm) S-waves, and diphasic T-waves. Lead IV was normal. In tracings (figure 3b) made with the arm wires reversed to "correct" for the dextrocardia the significant changes were the broad, notched P-waves in Leads I and II, the small (2 mm) S-waves, and the diphasic T-waves in Lead II, and the larger (3 mm) S-waves and diphasic (or inverted) T-waves in Lead III. There was a slight left axis deviation instead of a right axis deviation. Prolongation of the P-R interval persisted.

The patient was returned to her home physician, Dr. H. G. Heller, Hope, Ark., for treatment. She was not seen again except for a few minutes October 25 when the electrocardiograms reproduced here were made. Improvement was temporary and death occurred November 30, 1942.

### DISCUSSION

The history and physical findings, the demonstration of the location and configuration of some of the thoracic and abdominal organs by roentgenology, and the changes recorded by electrocardiography were diagnostic of dextrocardia with situs inversus.

There was adequate evidence for the diagnosis of chronic rheumatic aortic and mitral endocarditis. The history of an acute febrile illness resembling rheumatic fever was obtained. The physical findings of a pronounced systolic basal thrill and a loud well transmitted systolic and a distinct diastolic aortic murmur in a young person are diagnostic of chronic rheumatic aortic endocarditis. The characteristics of the first mitral sound and the systolic and diastolic murmurs heard at the cardiac apex were most suggestive of chronic mitral endocarditis in spite of the fact that the aortic manifestations were predominant. The fluoroscopic and roentgenographic findings of enlargement of the conus area of the right ventricle and of enlargement of the left auricle are the usual structural changes demonstrable in mitral stenosis. The broad, notched P-waves in Leads I and II of the electrocardiogram are indicative of left auricular strain and the T-wave changes in Leads II and III suggest right ventricular strain. Both of these are produced by mitral stenosis. The very slight left axis deviation instead of right deviation suggests that there was a predominant left ventricular strain such as is found in aortic lesions.

The prolonged P-R intervals present in the tracings taken on both September 14 and October 25, 1942 could be indicative of myocardial disease—There had been symptoms suggestive of recurrence of rheumatic fever a few weeks before our examination—The patient had been taking one cat unit of digitalis daily for approximately six weeks at the time of the last electrocardiographic examination. The dose at the time of the first cardiogram is not known.

The electrocardiograms were interesting and instructive. They revealed

- 1 Findings diagnostic of dextrocardia (Inversion of all complexes in Lead I)
- 2 Evidence of left auricular strain (Broad notched P-waves in Leads I and II)

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## EDITORIAL

### *LUMBODORSAL SYMPATHECTOMY FOR HYPERTENSION*

OPERATIONS on the sympathetic nervous system designed to relieve hypertension have aroused considerable interest for a number of years. Results from the majority of the earlier procedures were so variable that many surgeons and physicians became skeptical as to the possibilities inherent in this form of therapy. It is only in the past seven years that the more radical lumbodorsal sympathectomy developed by Dr. Reginald Smithwick has shown sufficiently good results to revive enthusiasm over the surgical treatment of hypertension.

The technic for the perfected operative procedure was published in 1940.<sup>1</sup> The purpose of the operation is to interrupt the vasomotor supply to the arterioles of the abdominal viscera. The two stages of the operation are performed about 10 days apart. The great splanchnic nerves are removed from the iliac ganglia to the midthoracic level and the sympathetic trunks are excised from at least the ninth dorsal to the first lumbar to at most the sixth dorsal to the third lumbar, inclusive. The operative mortality in Smithwick's hands has been less than 3 per cent in a series of over 500 cases, an unusually low rate considering the severity of the hypertensive disease in many of the patients.

Smithwick<sup>2</sup> noted that a significant and persistent lowering of the diastolic pressure followed operations of this order of magnitude in the majority of patients. This was associated with favorable changes in the eyegrounds, electrocardiograms, and cardiac and renal functions as well as in symptoms. The lowering of blood pressure was thought to be due to a decrease in the tone of arteriolar smooth muscle. Renal biopsies<sup>3</sup> from 100 hypertensive patients in the course of sympathectomy revealed no renal vascular disease or insignificant changes in 28 per cent and only mild changes in an additional 25 per cent. From these observations, it was concluded that the morphologic evidence of renal vascular disease in more than half the cases was inadequate to be regarded as the sole factor in producing the hypertension and that the hypertensive state antedated the renal vascular lesion.

On the whole, the results of the operation have been better in women than in men. Also, the results vary according to the type of hypertension with particular emphasis placed upon the width of the pulse pressure. Smithwick divided his patients into three types: narrow, intermediate, and wide pulse pressure, designated as Types 1, 2 and 3, respectively. In general,

<sup>1</sup> SMITHWICK, R. H. A technique for splanchnic resection for hypertension, *Surgery*, 1940, 1, 1-8.

<sup>2</sup> SMITHWICK, R. H. Surgical treatment of hypertension, *Arch. Surg.*, 1944, xlix, 180-192.

<sup>3</sup> CASTLEMAN, B., and SMITHWICK, R. H. The relation of vascular disease to the hypertensive state, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1256-1261.

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1. The first group of people who are interested in the results of the study are the researchers themselves. They want to know if the study was successful in achieving its goals and if the results are consistent with their expectations.

1. *Chlorophyll a* and *Chlorophyll b* were determined by the method of Arar and Collins (1971) using a Shimadzu 1601 UV-Visible Spectrophotometer. The concentration of chlorophyll was expressed in  $\mu\text{g mL}^{-1}$ .

begun to get into difficulties from their hypertension or have asymptomatic hypertension of extreme degree must be seriously regarded as potential candidates. They list the principal contraindications as follows: asymptomatic hypertension unless the blood pressure is extremely high, marked renal insufficiency, age over 50 years, chronic renal disease, coarctation of the aorta, and advanced arterial diseases. Although these are some of the more common reasons to advise against operation, they are not necessarily absolute, other contraindications will be found in individual cases. Among the preliminary studies which may be carried out while the patient is ambulatory, Thomas lists serologic test for syphilis, blood count, urine examination, blood non-protein nitrogen, sugar, and cholesterol, phenolsulfonphthalein test, electrocardiogram, teleoroentgenogram of heart, and intravenous pyelogram. After these studies have been completed, certain patients can be eliminated at once as candidates for sympathectomy. Those who still appear eligible should be admitted to the hospital as bed-patients for further investigation, provided the patient has signified his willingness to undergo surgery should he prove suitable. It is recommended that the following studies be carried out while the patient is hospitalized: urea clearance, urine concentration test, urine culture, photographs of optic fundi, chart of daily resting blood pressure, cold pressor test, sedation test, postural blood pressure response, vital capacity, venous pressure, circulation time, and cardiac output. Once this mass of clinical data has been assembled, the physician and surgeon together have a wealth of objective information on which to base their final decision as to the advisability of operation. It is important that candidates be worked up and operated upon as promptly as possible since certain patients may suffer from cerebral accidents while waiting for the studies to be completed.

Perhaps the invasion of the surgeon into the therapy of hypertension—staple of pure “medical” diseases since time immemorial—may come as a disturbing jolt to many an internist and cardiologist. But we internists must frankly confess that we have been able to accomplish relatively little in the alleviation of hypertension beyond teaching the unfortunate victim how to live with his disorder rather than to fret himself into a premature stroke. Therefore, let us graciously stand back and say, ‘More power to the surgeon!’ For, after all, the transfer of the therapy of hypertension to the surgeon may rightly be regarded as divine retribution for the manner in which the internist with his sulfonamides and penicillin has wafted many a potential victim away from the surgeon’s knife.

W H B

## REVIEWS

*Physical Foundations of Radiology* By OTTO GLASSER, Ph D, EDITH H QUIMBY, Sc D, LAURISTON S TAYLOR, Ph D, and J L WEATHERMAN, M A 426 pages 19 × 13.5 cm 1944 Paul B Hoeber, Inc, New York Price, \$5.00

Although it covers the field of physical radiology rather completely, it would be difficult to recommend this volume to roentgenologists. The several authors who have written this book must have done so for those who have had considerable training in radiation physics. Those who are not fortunate enough to have had such training will find this book incomplete in its explanations, and rather confusing. The writers plunge directly into physics (which at best is dull reading), neglecting to elucidate the more fundamental aspects of radiology. To one seeking knowledge of radiology, this lack of explanations causes the book to be very rugged reading.

Each author contributes several chapters to the volume, discussing many things, such as measuring roentgen units, the various ways of doing so, the biological effect of irradiation, tissue dose calculation, filtration of both roentgen-rays and radium. The cyclotron is mentioned and a brief discussion is added concerning the radioactivity of elements following bombardment by this machine. Radium and its various decomposition products are described, as well as filtration and tissue dosage of this element. As will be noted from this brief list of subjects covered many important matters are discussed. This would indeed be an excellent volume if the writers did not assume that the reader is quite conversant about radiation physics. It is not recommended.

D J B

*Fundamentals of Pharmacology* For Students and Practitioners By CLINTON H THIENES, M D, Ph D, Professor of Pharmacology, University of Southern California 497 pages, 15 × 22 cm 1945 Paul B Hoeber, Inc, New York 16, N Y Price, \$5.75

This text designed for students of medicine and physicians is an up-to-date volume. The aim of the author has been to reduce the large volume of pharmacologic literature to fundamentals and to present the material in concise terms. In the words of Dr Thienes the choice of material has been governed by the fact that pharmacology is taught before the medical student has had clinical experience, therefore, a complete discussion of therapeutic uses of drugs has not been attempted. The arrangement of the text is novel. Stimulants of the central nervous system are first considered and then the central nervous system depressants. In section three drugs acting on the peripheral nervous system are discussed followed by drugs acting on muscles, antiparasitic drugs, hormones, vitamins, locally acting substances, diagnostic agents, the action of drugs on cells and finally prescription writing. Following this plan one finds a discussion of digitalis under drugs acting on muscles, sulfonamides and antibiotics are considered in the section dealing with antiparasitic drugs, epinephrine, however, is considered in the section with sympathomimetic drugs and not with the hormones. With this condensed form the author has managed to preserve a readable style and even such subjects as cellular structure and metabolism in relation to pharmacology have received rather detailed consideration. The author is to be congratulated upon the text as a whole and teachers may recommend this book to students without reservation.

J C K Jr



## BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Fundamentals of Pharmacology* By CLINTON H. THILNLS, M.D., Ph.D., Professor of Pharmacology, University of Southern California School of Medicine. 497 pages, 15 × 22 cm. 1945. Paul B. Hoeber, Inc., New York. Price, \$5.75.

*Transactions of the Association of American Physicians*. Fifty-Eighth Session, held at Atlantic City, N. J., May 9, 1944. Volume LVIII. 1944. Published for the Association, Philadelphia. 204 pages, 15.5 × 23 cm.

*The Fundamentals of Electrocardiographic Interpretation*. Second Edition. By J. BAILEY CARTER, M.D., F.A.C.P. 406 pages, 14.5 by 21.5 cm. 1945. Charles C. Thomas, Baltimore and Springfield. Price, \$6.00.

*Constitutional Medicine and Endocrinology*. Edited by E. PULAY, M.D., A. P. CAWADIAS, O.B.E., M.D., F.R.C.P., and P. LANSEL, M.D. Volume I. 99 pages, 16 × 25 cm. 1944. 10s. 6d. net.

*Biological Symposia Vol. XI: Ageing and Degenerative Diseases*. Edited by ROBERT A. MOORE. 242 pages, 17.5 × 25 cm. 1945. The Jaques Cattell Press, Lancaster, Pa. Price, \$3.00.

*Universidad de Antioquia*. Numero 69. 1945. Medellin-Colombia.

*Myasthenia Gravis*. By ADALBERTO R. GOÑI. 1944. "El Ateneo". Buenos Aires.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

Since the publication of the last issue of the ANNALS OF INTERNAL MEDICINE, the following Fellows of the College have become Life Members

Dr Vernon L Evans, Aurora, Ill  
Dr Harry J Friedman, Seattle, Wash  
Dr Mark Alexander Griffin, Asheville, N C  
Dr William Ray Griffin, Asheville, N C  
Dr Sydney E Johnson, Louisville, Ky  
Dr Frank B Marsh, Salisbury, N C  
Dr Fred M F Meixner, Peoria, Ill

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### A C P MEMBERS IN THE ARMED FORCES

Dr Lawrence N Durgin, F A C P, Amherst, Mass, is a Major in the U S Army, having been on duty since July 15, 1941, but not previously recorded with the College. Reported in the June News Notes section of this journal was a total of 1,858 Fellows and Associates of the College on active military duty. In addition to Dr Durgin, the following members have since reported for active duty, bringing the total to 1,863

Joseph David Croft  
Robert A Edwards  
Clayton B Ethridge  
M Hill Metz

The following members of the College have been honorably discharged

Michael A Cogan, Captain, (MC), AUS—Springfield, Mass  
John B D'Albora, Lieutenant Colonel, (MC), AUS—Brooklyn, N Y  
A N Fregeau, Lieutenant Commander, (MC), USNR—San Francisco, Calif  
Lee Pettit Gay, Major, (MC), AUS—Lincoln, Nebr  
Robert Collier Page, Lieutenant Colonel, (MC), AUS—New York, N Y

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged

Irving L Applebaum, F A C P, Lieutenant Colonel, (MC), AUS—4 reprints  
Dr Benjamin M Bernstein, F A C P, Brooklyn, N Y—1 reprint  
Dr Harry R Litchfield, F A C P, Brooklyn, N Y—1 reprint  
Dr Thomas Hodge McGavack, F A C P, New York, N Y—4 reprints  
Dr Lawrence E Putnam (Associate) Washington, D C—1 reprint  
Dr Robert M Stecher, F A C P, Cleveland, Ohio—6 reprints

Dr John M Swan, F A C P, Rochester, N Y, on behalf of the New York State Committee of the American Society for the Control of Cancer, has donated to the College Library, Volumes 1 and 2 of "The Pith of Recent Cancer Literature"

## AUTUMN 1945 SCHEDULE, POSTGRADUATE COURSES

The Advisory Committee on Postgraduate Courses, with the approval of the Board of Regents, June 10, 1945, announces the following schedule of courses sponsored by the American College of Physicians during the autumn of 1945

ALLERGY—Roosevelt Hospital, New York City, Dr Robert A Cooke, Director, one week Oct 8-13

INTERNAL MEDICINE—University of Michigan Medical School, Ann Arbor, Dr Cyrus C Sturgis, Director, two weeks Oct 22-Nov 3

GENERAL MEDICINE—University of Oregon Medical School, Portland, Dr Homer P Rush, Director, one week Oct 29-Nov 3

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE—Massachusetts General Hospital, Boston, Dr Paul D White, Director, one week Nov 5-10

ADVANCED CARDIOLOGY—Philadelphia General Hospital, Philadelphia, Dr Thomas M McMillan, Director, one week Nov 26-Dec 1

ENDOCRINOLOGY—University of Illinois College of Medicine, Chicago, Dr Willard O Thompson, Director, one week Nov 5-10

GASTRO-ENTEROLOGY—University of Chicago, Dr Walter L Palmer, Director, one week Nov 12-17

The course "Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease" will be largely a repetition of a similar course given by Dr White during the autumn of 1944, when the course was greatly oversubscribed. Registrants who could not be accepted in 1944 for this course will be given first choice in 1945. A great host of registrations have already been received, owing to previous announcements in this journal, and it is already definitely established that the College will be unable to accommodate any non-members in this course—in fact, unless the Office of Defense Transportation removes present restrictions of fifty out-of-town registrants, the course must be considered filled to capacity.

The course in "Internal Medicine" at Ann Arbor will cover various phases of internal medicine and will be presented largely as an advanced course. The course will be valuable for returning physicians from the armed forces as a review course, for physicians preparing for American Board examinations, and practicing physicians desiring a refresher course. It will not be possible to register physicians except for the full course, that is, no registrations will be accepted for one week, for by so doing other physicians would be kept out.

The course in "General Medicine" at the University of Oregon Medical School will be primarily a repetition of the very fine course given at that institution for the College in 1944. A competent faculty and an excellent program have been organized. The selection of papers and subjects will be timely and interesting. Several special features will be arranged. Those taking the course previously were high in their praise. This course should be well supported by the College membership in the far western part of the United States and Canada.

The course in "Allergy" given by Dr Robert A Cooke will be largely a repetition of the excellent courses Dr Cooke has given repeatedly for the College during recent years. Nowhere in the country is such a valuable course available, condensed into a short period.

For the first time the College has organized and scheduled a course in "Advanced Cardiology," which will be open only to registrants with an adequate back-

ground in general cardiology. It will be presupposed that all registrants will be interested in the advanced phases of this specialty. The Director, Dr. McMillan, will supplement the local Philadelphia faculty with some outstanding authorities in the field from other cities and the registration will be held to a comparatively small group.

The course in "Endocrinology" by Dr. Willard O. Thompson is a repetition of other fine courses Dr. Thompson has organized and given for the College. His experience and enthusiasm are guarantees of the finest course procurable in this specialty.

The course in Gastro-enterology is organized to fill the steady demand for courses in this field. The Director, Dr. Palmer, will organize a course along sound and reliable principles, and a maximum registration is anticipated.

The Postgraduate Bulletin with registration forms will be mailed to all members of the College in the late summer or early autumn. Where facilities are available, courses will be open also to non-members of the College who have adequate preliminary training, preference to be given to non-members in the following order: (1) Candidates for membership, (2) Medical officers in the armed forces, (3) Physicians preparing for examinations by certifying boards, (4) Other non-members having adequate background for advanced work.

Especially is it the desire of the College to serve as many as possible of physicians retiring from active service in the armed forces. The Postgraduate Courses of the College are part of its war and postwar plans. The tuition fee for all courses will be: For members—\$20.00 per week, For non-members—\$40.00 per week, For medical officers of the armed forces of the United States and Canada—Free.

## REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

### Personnel Release Policy

Substantial releases of Army Medical Department personnel will not take place before the latter part of this year, Surgeon General Norman T. Kirk said in announcing a policy on discharges in conformity with War Department procedures. This is due to the fact that the peak of the Medical Department's activities will not be reached until fall.

In formulating the policy, consideration was given to civilian needs for professional medical, dental and veterinary care without weakening military needs. Other factors considered were the length of time necessary for personnel to complete their work in the Mediterranean and European Theaters and return to the United States, replacement of Medical Department personnel in active theaters by those who have not had overseas duty, necessity for the maintenance of a high standard of medical care, the heavy load of patients in the United States, evacuation of the sick and wounded from Europe in the next 90 days and continuing medical service in the Pacific.

The policy applies with equal effect to Army medical officers assigned to the Veteran's Administration and other agencies.

### *Medical Corps*

- a Officers whose services are essential to military necessity will not be separated from the service.
- b Officers above 50 years of age whose specialist qualifications are not needed within the Army will receive a high preferential priority for release from active duty.
- c Adjusted Service Ratings will be utilized as a definite guide to determining those who are to be separated.

• Acting Secretary of War Patterson and General Kirk Report on Health of Army

Honorable Robert P. Patterson, Acting Secretary of War, in presenting Major General Norman T. Kirk, F. A. C. P., Surgeon General of the Army, at a radio and press conference on May 24, made the following points

Despite the problems of fighting in virtually all parts of the world and in caring for the largest American Army in history, no army at any time in history has achieved a record of recovery from wounds and freedom from disease comparable to that of the American Army in this war, 97 out of every 100 men wounded in battle who reach a hospital have been saved, 70 out of every 100 men wounded overseas were returned to duty and 27 were evacuated to this country, during the past three years less than one death per 1,000 men per year has resulted from disease, malaria has been reduced from hundreds of cases per 1,000 men per year to less than 50, the dysenteries have occurred among less than 90 among every 1,000 men per year and have been readily controlled, physical examinations are being given to each of the 3,500,000 soldiers in the European and Mediterranean theaters before they are re-deployed, Medical Department personnel will be sent to the Pacific in ever-increasing numbers, the peak of the Medical Department's activities will not be reached until autumn, 1945, wounded and sick are being returned to this country from all theaters at the rate of 44,000 per month, 7 additional hospital ships, bringing the total to 29, with an aggregate patient capacity of 20,000, have been provided for the evacuation of patients from Europe to this country; special hospital equipment has been placed aboard 24 troop transports, giving the Army an additional patient-carrying capacity of 40,000, 8,000 patients a month are being brought back to the United States by plane, the population of all Army hospitals in the United States at present is 290,000, which is expected to reach 315,000 by September

Mr. Patterson said in part

"No greater tribute can be paid to the Medical Department of our Army than the tribute paid by its record of saving lives in this war."

General Kirk reported in part as follows

"The Army Medical Department is well prepared to maintain its record of saving lives and guarding against disease in the second phase of World War II which will be centered in the Pacific. As combat activities increase in that area troops moved from European theaters will find a different type of warfare, different diseases and different methods of combating disease.

"The Medical Department has been preparing for years for its fight on disease in the Pacific. In addition to its intensive research into diseases common to that area it has gained much value in practical application of its methods from the campaigns already fought.

"In the Pacific areas our fighting men are exposed to many types of disease that are rare in the United States and Europe. However, this should not be considered cause for alarm. With proper preventive measures and medical service the disease rate in the Pacific will be kept to a minimum.

"Every fighting unit in the Pacific area has had the same type of medical organization accompanying it as those in other theaters. The chain of evacuation of the wounded is well organized and is very effective. Because of geographical and climatic differences certain changes were desirable, but the same high type facilities are available.

"The main diseases to be encountered in the Pacific are malaria, the dysenteries, scrub typhus, skin infections, schistosomiasis, filariasis and dengue fever. Excellent progress has already been made in keeping the incidence of all of these diseases to a very low degree.

"Malaria, for example, has been reduced to one-fourth its incidence in the early part of the war so that the overall death rate from malaria in the Army is 01 per cent.

"The use of D D T and atabrine is primarily responsible for lowering the incidence rate of the most disabling tropical diseases. The remarkable record in lowering the malaria rate is due also to strict discipline and control measures. Malaria is spread by the anopheles mosquito. D D T, a recently developed insecticide, is used to kill this mosquito and the larva. Areas are sprayed with D D T by plane and a five per cent solution of D D T sprayed on barracks walls in kitchens and huts kills all mosquitoes and flies alighting thereon for months after spraying.

"The dysenteries, so common in the Pacific areas, which are spread by flies are also rendered less prevalent by the use of D D T.

"Atabrine has been found more effective as a therapeutic agent in the control of malaria than quinine.

"Filariasis, which is also spread by the mosquito, is reduced by the use of D D T and mosquito control methods.

"Schistosomiasis is caused by a small fluke found in pools and running streams which in a matter of seconds burrows through the skin and infects the individual. All water found to contain these flukes is posted and personnel is warned not to bathe, wade or wash in it.

"Areas found to contain scrub typhus are immediately burned over, clothing is impregnated, and efforts are being made to develop a vaccine to counteract it.

"Dengue fever, also spread by the mosquito, is controlled by the use of D D T and mosquito abatement.

"It can readily be noted that D D T is one of the miracle developments of this war.

"Last year a tropical disease center was opened by the Army Medical Department at Moore General Hospital, Swannanoa, North Carolina. It was designated as a center for the study and treatment of tropical diseases. This center has assisted greatly in the investigation and treatment of these diseases and has reduced the loss of manpower as a result of illness, thereby making an important contribution to the continuing improvement of American medicine.

"In addition to protecting the soldier from diseases of the tropics the Army Medical Department is affording all possible protection against disease and harmful pests which might be brought into the United States by military traffic. This is done through a quarantine branch which works in conjunction with the U S Public Health Service and the Navy.

"The Army program includes measures to prevent the importation of dangerous insects from abroad. Extensive insect control programs have been carried out about military stations and airports abroad, using highly effective techniques and agents. Passengers, planes, ships and cargo are sprayed with insecticides in order to eliminate insect risk.

"The battle is also waged through the control of rats and vermin. The most effective means of ridding ships of rats has been to build ships in such a way that rats cannot live or breed aboard them. Modern American ships are practically free of this age-old problem.

"To protect the country against agricultural diseases and pests which might be imported, rigid restrictions and inspections are made fully effective for military traffic. Particular stress is laid upon packing materials which might harbor insect forms.

"The Army Medical Department has complete medical and sanitary surveys of all the territory in the Pacific which is potential battle ground. The health hazards to soldiers are known to the Medical Corps officers who accompany all invasion troops and that knowledge is distributed to all the men.

"The Army Medical Department has been doing a fine job in the Pacific and will continue to do that job as activities in that theater increase. It is true that the

pestilential islands of the Pacific have not been changed into gardens of Eden, but when the deplorable health conditions that existed there are compared with what has been accomplished it is obvious that our victory over the Japs will be hastened

"While all of this work and planning was going on for the increased activity in the Pacific the Army Medical Department during 1944 took care of 4,435,000 patients in hospitals—2,315,000 in the United States and 2,120,000 in hospitals overseas. In addition it provided care for an additional 43,210,000 non-hospitalized patients—those with minor infections and injuries who were only temporarily incapacitated

"It performed the essential functions of caring for men wounded in battle, the injured and the sick to maintain fighting strength with 45,000 medical corps, 15,000 dentists, 52,000 nurses, 2,000 veterinarians, 18,700 medical administrative corps men, 2,500 sanitary corps specialists, 1,000 physical therapists, 1,500 dietitians, 61 pharmacy corps officers, 535,000 enlisted medical aid men and approximately 80,000 civilian employees

"Illness and recuperation of wounded and injured men does not cease with a formal declaration of the end of hostilities on any front. The care of these men and women is a continuing responsibility of the Medical Department which will go on for many months in the future. It will increase rather than diminish during the remainder of 1945, according to the best estimates which can be made now. Therefore, as I have said before, medical care by the Army has yet to hit its full stride. One thing I wish to promise is that the best scientific medical attention will continue to be furnished to every man needing it"

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#### Colonel Eppinger Returns to U S

Colonel Eugene Eppinger (Associate), (MC), AUS, formerly of Brookline, Mass., recently returned to this country from the Philippines where he was Assistant Consultant in Medicine in the Southwest Pacific Area of Operations

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#### Colonel Youmans and Dr Wearn Survey Pacific Area Nutrition Problems

Colonel John B. Youmans, F A C P, Director of the Nutrition Division, Preventive Medicine Service, Office of The Surgeon General, and Dr Joseph T. Wearn, F A C P, of Cleveland, Civilian Consultant to The Surgeon General, returned in May from an extended nutritional survey of the islands in the Pacific Ocean area during which they consulted with General MacArthur. They instituted a study on the nutrition of troops in the area and on diseases which may have a nutritional origin

#### Recent Promotions, Medical Corps Officers

##### *Lieutenant Colonel to Colonel*

John Sinclair Denholm (Associate), Burlington, N C

##### *Major to Lieutenant Colonel*

Lee Heiman Leger (Associate), Kansas City, Kan  
George Carson McEachern (Associate), Long Island, N Y  
Arthur Dale Nichol, F A C P, Shaker Heights, Ohio  
Oscar Armand Palatucci (Associate), New York, N Y

### PHILIPPINE BUREAU OF SCIENCE TOTALLY DESTROYED

The Philippine Bureau of Science, Manila, which was the principal center of research work in the Philippines, is reported to have been totally destroyed by the Japanese. This bureau housed the most important scientific library in the islands and was the publication headquarters of the Philippine Journal of Science. It contained thousands of specimens of Philippine and other Asiatic plants, birds, mammals, insects, etc. The School of Medicine, the School of Hygiene and Public Health and the entire plant of the University of the Philippines, the Philippine General Hospital, the Weather Bureau and the Philippine National Library were located in the same general area, and these buildings, for the most part, and everything of scientific value, have been destroyed or very badly damaged.

### PENICILLIN TABLETS FOR CIVILIAN USE NOW AVAILABLE IN MEXICO

For the first time penicillin in tablets for commercial purposes has gone on sale. U S producers of penicillin must await lifting of the W P B restrictions before they can begin producing the drug in pills and ointments for commercial purposes. However, the Mexican government has granted permission to its sole commercial producer, Wyeth-Stille, S A, of Mexico City, affiliate of Wyeth Incorporated of Philadelphia, to manufacture penicillin in tablets and make them available for civilian use immediately. The tablet is packed in vials containing five tablets of 20,000 units each. The vials contain a desiccant which absorbs moisture, allowing the penicillin to remain stable for six months or more, it is claimed. Just as soon as W P B gives permission, penicillin for oral administration will be placed on the market in the United States.

### ELECTIONS TO A C P MEMBERSHIP BY BOARD OF REGENTS,

PHILADELPHIA, JUNE 10, 1945

#### *Elections to Fellowship*

Annis, Jere Wright, Lakeland, Fla, AUS

Banks, Roland Wellington, Philadelphia, Pa, AUS

Bardon, Richard, Duluth, Minn

Beckwith, Julian Ruffin, Charlottesville, Va, AUS

Benson, Otis Otto, Jr, U S Army

Bondurant, Charles Palmer, Oklahoma City, Okla

Bradford, Aubrey LeVerne, U S Army

Broun, Coronwy Owen, St Louis, Mo

Campbell, Donald Clarence, Rochester, Minn, AUS

Chamberlain, Eugene Charles, Fort Lauderdale, Fla

Chamberlin, Donald Tillinghast, Boston, Mass, AUS

Coffelt, Ralph L, Waco, Tex, USNR

Crandall, Lathan Augustus, Jr, Germantown, Tenn

Dearing, William Hill, Rochester, Minn

Detweiler, Herbert Knutsen, Toronto Ont, Can

Dock, William, New York, N Y

Dolger, Henry, New York, N Y



Dreessen, Waldemar Claus, U S Public Health Service  
Durham, J(ames) Richard, Jr , Wilmington, Del , AUS

Elliott, F(rederick) George, Edmonton, Alta , Can , RCAMC

Fenn, George Karl, Chicago, Ill  
Ferguson, John Howard, Chapel Hill, N C  
Fennis, Eugene Beverly, Jr , Cincinnati, Ohio

Garrison, George Harry, Oklahoma City, Okla  
Ginsberg, Harold Isadore, Detroit, Mich , AUS  
Graham, William Donald, U S Army  
Graves, Herman Coddington, Grand Junction, Colo  
Gubnei, Richard Sigmund, Brooklyn, N Y

Hamilton, Charles Edward, Lafayette, La  
Hemphill, Roger Andrew, Mt Morris, N Y  
Hill, Joseph MacGlashan, Dallas, Tex  
Hobbs, Robert Emmett, Shenandoah, Pa , AUS  
Hoxie, Harold Jennings, Los Angeles, Calif

Kalkstein, Mennasch, New York, N Y , AUS  
Karr, J(ohn) Kenneth, Milwaukee, Wis  
Kauvar, Solomon Salkind, Denver, Colo  
Keane, Roger Hunter, Portland, Ore , USNR  
Keliher, Thomas Francis, Washington, D. C  
Kendell, H(erbert) Worley, Chicago, Ill , USPHS (R)  
Kiene, Hugh Edward, Providence, R I , AUS  
Kinsell, Laurance Wilkie, East Stroudsburg, Pa , USNR  
Kinsey, Harold Ivan, Toronto, Ont , Can  
Kirshbaum, Jack D , Chicago, Ill , AUS  
Krell, Solomon, New York, N Y

Leinoff, Harry D , New York, N Y , AUS  
Leonard, John Charles, Hartford, Conn  
Lidman, Bernard Isaac, Norfolk, Va , AUS

Mackay, Roland Parks, Chicago, Ill  
Marion, Donald Feige, Detroit, Mich , AUS  
Matthews, Robert Archibald, Philadelphia, Pa  
Matzner, Milton John, Brooklyn, N Y , USNR  
Mays, John Richard Shannon, Milledgeville, Ga , AUS  
McCombs, Robert Pratt, Jenkintown, Pa , USNR  
McHardy, George Gordon, New Orleans, La  
McManus, John Francis, Boston, Mass , AUS  
McReynolds, Ralph, Quincy, Ill  
Meyer, Paul Reims, Port Arthur, Tex  
Miller, David Kimball, Buffalo, N Y  
Miller, Raymond Everett, New York, N Y , USNR  
Millman, Max, Springfield, Mass  
Mitchell, William John, Los Angeles, Calif , AUS  
Moore, George Barnard, Jr , U S Army  
Murphy, Martin Alvin, Brooklyn, N Y  
Murphy, Willis Aloysius, New York, N Y , USNR

Noth, Paul Henry, Grosse Pointe Farms, Mich

Oigain, Edward Stewart, Durham, N C

Parsons, Ernest Holden, U. S Army

Paulus, David Dare, Oklahoma City, Okla

Perlman, Frank, Portland, Ore, AUS

Query, Richard Zimri, Jr, Charlotte, N C, AUS

Rascoff, Henry, Brooklyn, N Y

Rash, Jack Otway Watkins, Miami, Fla, AUS

Richards, Dickinson Woodruff, Jr, New York, N Y

Robinson, Albert Henry, U S Army

Robinson, William Dodd, Ann Arbor, Mich

Ross, Harry Plummer, Richmond, Ind

Ryan, Joseph Maurice, St Paul, Minn, AUS

Schweiger, Lamont R, Milwaukee, Wis, AUS

Serra, Lawrence Mario, Baltimore, Md

Shaw, James Raymond, U S Public Health Service

Sherman, E(dward) David, Sydney, N S, Can

Silvers, Seymour Harry, Brooklyn, N Y

Slutzky, Ben, Omaha, Nebr

Smith, David Tillerson, Durham, N C

Smith, Lucian Anderson, Rochester, Minn, AUS

Spessard, Thomas Nathaniel, Norfolk, Va, USNR

Sprunt, Douglas Hamilton, Memphis, Tenn

Stringer, Christopher James, Lansing, Mich

Thomas, George Carroll, U S Navy

Tiber, Arthur Martin, New York, N Y, AUS

Tillman, Richard Nelson, Baltimore, Md

Twiss, Arthur Raymond, Oakland, Calif, AUS

Valdez, Frank Carl, Chicago, Ill

Vander Veer, Joseph Bedford, Philadelphia, Pa, AUS

Vass, Aloysius, Springfield, Ill, AUS

Warren, Leon Hugh, Washington, D C, AUS

Williams, Alton Floyd, Metter, Ga, AUS

Wintrobe, Maxwell Myer, Salt Lake City, Utah

Wood, W(illiam) Barry, Jr, St Louis, Mo

Woody, McIver, New York, N Y

Wright, Scheffel Hays, Miami, Fla

#### *Elections to Associateship*

Alpher, Isadore Meyer, Washington, D C

Baker, Elsworth Fredrick, Marlboro, N J

Barker, Charles Scott, Montreal, Que, Can

Barker, Joseph Michael, Washington, D C

Baube, John Louis, Mt Vernon, Ohio, AUS  
Bayles, Theodore Bevier, Boston, Mass, AUS  
Beebe, John Taylor, Hartford, Conn  
Bender, Morris Boris, New York, N Y, USNR  
Bennett, Raymond Edward, St John's, Newfoundland  
Berry, Maxwell Glen, Kansas City, Mo, AUS  
Bishop, Ernest Wade, Providence, R I  
Bosse, Milton Dietrick, Pittsburgh, Pa  
Brethauer, Edward Albert, Jr, Pittsburgh, Pa  
Brown, Morton Goodwin, Boston, Mass, AUS  
Burdon, Phyllis Josephine, Seattle, Wash  
Butler, Fred Arthur, U S Navy

Cannon, Jesse Floyd, Salt Lake City, Utah  
Cantor, Mortimer Jacob, Brooklyn, N Y, AUS  
Chinn, Austin Brockenbrough, Washington, D C, AUS  
Connor, Charles Ashley Richard, New York, N Y, AUS  
Crowe, William Roland, Jr, Atlanta, Ga

Doak, Edmond King, Houston, Tex  
Donohue, William Michael, Houston, Tex, AUS  
Durkee, Ralph Everett, Jr, Hartford, Conn, USPHS (R)

Edgar, Irving Iskowitiz, Detroit, Mich

Feinstein, Marcus Abraham, New York, N Y, AUS  
Finegan, Rexford William, New York, N Y, AUS  
Flaum, Gerald, New York, N Y, USNR  
Fleishman, Alfred, St Louis, Mo, AUS  
Fleiss, Arthur Nathan, Syracuse, N Y  
Freireich, Abraham Walter, Malverne, N Y  
Friedgood, Harry Bernard, Los Angeles, Calif

Gold, Rubin Leonard, San Francisco, Calif, AUS  
Goldner, Martin Gerhard, Chicago, Ill, AUS  
Gordon, Marie Dannenbauer, San Antonio, Tex  
Greist, John Howard, Indianapolis, Ind, AUS  
Gunther, Lewis, Los Angeles, Calif, USNR

Hammerstrom, Carl Frederick, Jamestown, N Y, AUS  
Hampton, Hiram Phillip, Tampa, Fla, AUS  
Hanss, Armand William, Springfield, Mo, AUS  
Havell, Robert Barron, Washington, D C  
Hawirko, Leonora, Edmonton, Alta, Can  
Heineken, Theodore Stanley, Bloomfield, N J, AUS  
Hodas, Joseph Henry, New York, N Y, USNR  
Hoffman, Samuel J, Chicago, Ill, AUS  
Horner, John Linscott, St Louis, Mo  
Hull, Wayne McKinley, Omaha, Nebr  
Hyman, Samuel, Utica, N Y

Johnson, Artell Egbert, New York, N Y  
Johnson, Ralph Arthur, Detroit, Mich

Katz, Sol, Washington, D C  
 Knudson, Alvin Bernt Clifford, Dwight, Ill , AUS  
 Kohlstaedt, Kenneth George, Indianapolis, Ind  
 Korth, Zeno Nicholas, Omaha, Nebr , AUS  
 Kreitz, Paul Brooks, Bethlehem, Pa  
 Krygier, John Joseph, Portland, Ore  
 Kugel, Victor Harris, New York, N Y , AUS

Lamb, John Henderson, Oklahoma City, Okla  
 Laufer, Srul Tul, Halifax, N S , Can  
 Leary, William Vincent, Rochester, Minn , AUS  
 Lease, Raymond Essex, Oyster Bay, N Y  
 Leech, Elfred Llewellyn, Oneonta, N Y  
 Lenton, Herbert P , Carlisle, Pa , AUS  
 Levin, William Cohn, Galveston, Tex  
 Lindauer, Max August, Philadelphia, Pa , AUS  
 Lubitz, Joseph M , Chicago, Ill USPHS (R)  
 Lueck, Arthur George, U S Navy

Macdonald, James William, Detroit, Mich  
 Marra, John James, Albany, N Y  
 Mauser, Carl Louis, Berkley, Calif  
 McKinley, Wesley Frank, Jr , Galveston, Tex  
 McLemore, Harold Hiques, Spokane, Wash , AUS  
 Mendlowitz, Milton, New York, N Y , AUS  
 Miller, Sidney, Rochester, Minn , AUS  
 Moss, John Edward, U S Navy  
 Murphy, Franklin David, Philadelphia, Pa , AUS

Palatucci, Oscar Armand, New York, N Y , AUS  
 Paris, Marcus, South Norwalk, Conn  
 Paul, Jerome Thomas, Chicago, Ill , AUS  
 Payne, Russell Crandle, Washington, D C  
 Prigal, Samuel Jeremiah, New York, N Y

Rawling, Frank Frederick Archibald, Ann Arbor, Mich  
 Resch, Joseph Anthony, U S Army  
 Rice, Raymond Lester, Milwaukee, Wis  
 Robertson, Elmer Shackleford, Richmond, Va , AUS  
 Rodriguez-Ollerios, Angel, San Juan, P R  
 Rogers, Hobart, Oakland, Calif  
 Ryan, Edward Joseph, Cleveland, Ohio, USNR

Salmon, George Wilbur, Houston, Tex  
 Sanders, Alexander, Chicago, Ill , AUS  
 Schaefer, Bertram Francis, Washington D C  
 Schwartz, Robert, Aspinwall, Pa , AUS  
 Shullenberger, Wendell Arthur, Indianapolis Ind  
 Silverman, Jacob Joseph Staten Island, N Y , AUS  
 Simpson, Roger Graham, San Francisco, Calif AUS  
 Sklaver, Joseph, Waterbury, Conn . AUS  
 Sokolow, Maurice, San Francisco, Calif , USNR  
 Straumfjord, Jon Vidahn, Astoria, Ore

Vidgoff, Ben, Portland, Ore  
 Vynei, Harold Lawrence, Bientwood, N Y, AUS

Walker, Edmund Frank, Worcester, Mass, AUS  
 Weedon, Frederick Renfroe, Jamestown, N Y  
 Weig, Clayton George, Buffalo, N Y  
 Westra, Jacob John, Champaign, Ill  
 Wexler, Jack, Boston, Mass, AUS  
 Wheeler, William Louis, Jr, New York, N Y  
 Wilson, Sloan Jacob, Columbus, Ohio, AUS  
 Wright, Jackson White, Cincinnati, Ohio, AUS

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Lieutenant Colonel Kendall Elsom, F A C P, is now Chief of the Medical Service at the Regional Hospital of the Army Service Forces at Fort Benning, Ga

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Lieutenant Colonel Charles M Caravati, F A C P, Chief of the Medical Service at the Woodrow Wilson General Hospital, Staunton, Va, addressed the Luzerne County Medical Society, May 16, on "The Regional non-Malignant Ulcerative Lesions of the Bowel"

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Dr Bernard L Wyatt, F A C P, for many years located at Tucson, Arizona, opened offices in the Fidelity Building, Los Angeles, California, on June 1

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On March 2, 1945, Dr Howard Wakefield, F A C P, and Dr Selim W McArthur, Chicago, presented a paper, "Further Observations on the Electrocardiogram during Experimental Distention of the Human Gall Bladder," before the Chicago Surgical Society

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On May 10, 1945, Dr Herbert T Kelly, F A C P, Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, presented before the Centre County Medical Society at Nittany Lion, State College, Pa, a paper on "Convalescent Care and Postoperative Management"

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Dr Theodore Rothman (Associate), formerly of Paterson, N J, during May removed to Los Angeles where he opened his office for the practice of medicine at 2007 Wilshire Boulevard

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#### MEDICO-LEGAL CONFERENCE AND SEMINAR OCTOBER 1-6, 1945, AT BOSTON

The Department of Legal Medicine of the medical schools of Harvard, Tufts, and Boston University in association with the Massachusetts Medico-Legal Society will present a six-day program of lectures, conferences, and demonstrations having to do with the investigation of deaths in the interests of public safety Attendance during five of the six days of the course will be limited to fifteen persons who have registered in advance On one day (October 3) the program will be open to any physician, lawyer, police official, or senior medical student who may care to attend

Further information may be obtained from the Secretary of the Massachusetts Medico-Legal Society, 25 Shattuck Street, Boston

Lieutenant Colonel Leo V Schneider, F A C P, Associate Clinical Professor of Medicine at Georgetown University School of Medicine, Washington, and Chief Medical Officer at Glenn Dale Sanatorium, Glenn Dale, Md, was recently made Chief of Industrial Medicine at the New York Port of Embarkation

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Captain Lloyd R Newhouser, F A C P, delivered the 1945 Kober Foundation Lecture on "The Rôle of Whole Blood Plasma and Plasma Fractions in War Medicine" at Georgetown University School of Medicine, Washington, March 28 This marked the birthday of the late Dr George M Kober, F A C P, who for many years was Dean of that institution and founder of this lecture Captain Newhouser received an honorarium of \$500 Vice Admiral Ross T McIntire, Surgeon General of the Navy, presided

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Dr Norman H Jolliffe, F A C P, has been made Chief of a new city-wide nutrition clinic at the lower East Side Health and Teaching Center of New York City

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Dr Carl J Wiggers, F A C P, and his associates in the Department of Physiology, Western Reserve University, Cleveland, have received a grant of \$8,200 from the Commonwealth Fund to continue studies on the peripheral circulation and shock during 1945-1946

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Captain Forrest M Harrison, F A C P, Chief of the Neuropsychiatric Division of the National Naval Medical Center, Bethesda, Md, has been given a special assignment to write the history of psychiatry in the Navy during World War II

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#### CAPTAIN ROLLAND R GASSER RECEIVES BRONZE STAR

Captain Rolland R Gasser, F A C P, formerly of Brooklyn, has been awarded the Bronze Star "for meritorious service to the United States as medical officer in command of a fleet hospital in the South Pacific area from March 31, 1944, to April 7, 1945 During this period Captain Gasser displayed exceptional ability in handling the many detailed medical problems which arose and worked tirelessly to establish and maintain excellent operating conditions throughout his command By his initiative and thorough knowledge of medical administration he effected an efficient hospital service for the sick and wounded in the South Pacific and evacuees from adjacent areas His leadership and professional skill were in keeping with the highest traditions of the United States Naval Service"

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#### THE MALCOLM T MACEachern AWARD

The Johnson and Johnson Research Foundation recently created an annual award at Northwestern University consisting of a silver medal and an honorarium of \$250 to be known as the Malcolm T MacEachern Award, in honor of Dr MacEachern a Fellow of the American College of Physicians, who is Associate Director of the American College of Surgeons and Director of the Program in Hospital Administration at Northwestern University Johnson and Johnson has also announced a five-year grant of \$75,000 to the program in hospital administration, including scholarships, to supplement \$15,000 granted two years ago

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Dr John F Kenney, F A C P, Pawtucket, R I, has been installed as President of the New England Conference of Industrial Physicians

Dr Frederick A Willius, F A C P , Rochester, Minn , addressed the 76th Annual Session of the Canadian Medical Association at Montreal, June 11-15, his subject being "Critical Evaluation of Methods of Diagnosis in Cardiac Disease, with Special Reference to Electrocardiography"

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Dr Samuel J McClendon, F A C P , San Diego, was recently made President-Elect of the California Medical Association

Dr Harry L Arnold, Jr (Associate), of Honolulu, was one of the guest speakers at the meeting of the Association, his title being "The Diagnosis of Early Lepromatous and Neural Leprosy"

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Dr Leroy E Burney (Associate), Regional Director of the U S Public Health Service, New Orleans, has been named State Health Commissioner and Secretary of the Indiana State Board of Health, his services having begun July 1, 1945

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Dr Lewis J Moorman, F A C P , Oklahoma City, has been reelected Secretary-Treasurer of the Oklahoma State Medical Association and will continue as Editor of its journal

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Dr Howard T Karsner, F A C P , Professor of Pathology and Director of the Institute of Pathology, Western Reserve University, Cleveland, addressed the Los Angeles Academy of Medicine, May 11, on "Tumors of the Endocrine Glands"

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Dr Charles Walter Clarke, F A C P , Executive Director of the American Social Hygiene Association, New York, has been reelected Vice President of the National Health Council

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Dr Russell H Oppenheimer, F A C P , as of June 1 resigned as Dean of Emory University School of Medicine, Atlanta. He had held the appointment for twenty years. Dr Oppenheimer will continue his work as Professor of Clinical Medicine.

Dr Eugene A Stead, Jr, F A C P , will serve as Acting Dean. Dr Stead is also Professor of Medicine and Chairman of the Department.

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Commander J Roscoe Miller, F A C P , Dean of Northwestern University Medical School, Chicago, is currently in charge of the Section on Internal Medicine, Professional Division of the Bureau of Medicine and Surgery, Washington, D C. Upon his release from service, he will serve as Medical Director of the Chicago and Northwestern Railroad, in addition to his deanship at Northwestern University.

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Dr Joseph S Evans, F A C P , will retire as Professor of Medicine at the University of Wisconsin Medical School at the end of the current semester. He was the school's first professor of medicine. He is also Chairman of the Department of Medicine and has been with that institution since 1909.

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#### EXAMINATIONS IN PEDIATRICS

The American Board of Pediatrics will conduct its fall written examination in various cities, under a monitor, October 19, 1945. The oral examination will be held in New York City, December 7-8, 1945.

Address the secretary, Dr C Anderson Aldrich, 115½ First Avenue, S W , Rochester, Minn , for further details

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Captain Lyle J Roberts, (MC), U S N , F A C P , is reported still to be a prisoner of war of the Japanese, probably located in Manchukuo

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Commander William M Silliphant, (MC), U S N (Associate), was among medical officers rescued from Bilibid Prison Camp in Manila He is now located at 129 N Santa Anita Street, San Gabriel, Calif , but will soon be reassigned to new work in the Navy

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Dr William C Chaney, F A C P , Memphis, was installed on April 8 as President of the Tennessee State Medical Association

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A Research Fellowship in Internal Medicine is being established at the University of Texas Medical Branch, Galveston in honor of Dr Marvin L Graves, F A C P , Emeritus Professor of Internal Medicine

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#### A POST-WAR PROGRAM FOR THE AMERICAN COLLEGE OF PHYSICIANS

At a meeting of the Board of Regents of the College at its headquarters in Philadelphia, June 10, 1945, much time was devoted to the consideration of a special educational program connected with the post-war planning of the College The detailed minutes will be published in the next issue of this journal

The Board of Regents proposed to employ an Educational Director to work under the Executive Secretary The proposed programs of the Committee on Fellowships and Awards, the Advisory Committee on Postgraduate Courses, the Committee on Educational Policy and the Committee on Post-War Planning for Medical Service will be correlated One of the chief aims of this program will be to offer assistance to members of the College returning from active military service The program of Postgraduate Courses, both of the short refresher and longer review types, will be considerably multiplied in 1946, a service will be initiated to help College members returning from the war to locate residencies, assistantships, teaching appointments, or places of practice The College will resume granting four or five annual Research Fellowships and a sum of \$25,000 has been appropriated for the establishment of Clinical Fellowships

The American College of Physicians has the machinery ready, from several years of experience, to administer this extended program Its aim is to offer to its members a personalized, intelligent and effective service No medical society has a more honored and respected reputation for effective work in the educational field It is hoped that foundations and some of the leading manufacturers of pharmaceuticals and medical supplies and publishers may wish to assist in this program by making grants to the College so that the maximum objectives may be attained

It should be understood however, that the College will continue to participate in the activities of the central Committee on Post-War Medical Service, consisting of the American College of Surgeons, the American Medical Association, the American College of Physicians and several other agencies The central committee, meeting monthly at Chicago is conducting a most worthy national program, perhaps of a less specific character, but more along the line of public relations and national principles The minutes of the national Committee on Post-War Medical Service are not at this time repeated in this journal because they have been published recently in the Journal of the American Medical Association



## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 1 (Maine, New Hampshire, Vermont, Massachusetts) and REGION No 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr W R Ohler, Chairman, Dr L E Parkins, Secretary, Dr S B Weld, Dr A M Burgess, Dr C S Keefer, Dr F T Hill, Dr J P Bowler, Dr B F Cook, Executive Committee members

*Station Hospital, Dow Field, Bangor, Maine*

July 17 Fractures of Extremities and Pelvis Joint Injuries  
August 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum

*Dispensary, U S Naval Air Station, Brunswick, Maine*

July 19 The Use of Penicillin and Sulfa Drugs  
August 16 Recent Advances in Diagnosis and Treatment of Diseases of the Central Nervous System

*Station Hospital, Fort Williams, Portland, Maine*

July 19 Acute Abdominal Emergencies  
August 16 Acute Hepatitis Its Diagnosis and Treatment (Pathological Physiology).

*Station Hospital, Presque Isle, Maine*

July 19 Hypertensive Cardiovascular Disease, Rheumatic Heart Disease, Treatment and Rehabilitation  
August 16 Diagnosis and Medical Treatment of Biliary Tract Lesions Surgical Treatment of Biliary Disease

*Station Hospital, Greiner Field, Manchester, New Hampshire*

July 18 Diagnosis and Medical Treatment of Biliary Tract Lesions Surgical Treatment of Biliary Disease  
August 15 Diagnosis and Treatment of Skin Diseases

*U S Naval Hospital, Portsmouth, New Hampshire*

July 19 Diagnosis and Treatment of Skin Diseases  
August 16 Recent Advances in the Treatment of Mental Diseases and Management of Psychoneuroses

*Regional Hospital, Waltham, Massachusetts*

July 19 Tumors of the Central Nervous System and Neurological Syndromes  
August 16 Cardiac Emergencies, Diagnosis and Treatment

*U S Naval Hospital, Chelsea, Massachusetts*

July 19 Diagnosis and Treatment of Skin Diseases  
August 16 Cardiac Emergencies, Diagnosis and Treatment

*Lovell General Hospital, Fort Devens, Massachusetts*

July 19 Blood Transfusions, Whole Blood and Derivatives, and the Rh Factor  
August 16 Acute Abdominal Emergencies

*Station Hospital, Camp Edwards, Massachusetts*

July 19 Cardiac Emergencies, Diagnosis and Treatment  
August 16 Contagious Diseases and Complications

*Cushing General Hospital, Frammingham, Massachusetts*

- July 19 Acute Infections of the Central Nervous System  
 August 16 Fractures of Extremities and Pelvis Joint Injuries

*Station Hospital, Camp Myles Standish, Taunton, Massachusetts*

- July 19 Pilonidal Sinus and Common Diseases of the Anus and Rectum  
 August 16 Thyroid, Pituitary and Adrenal Diseases Ovarian and Testicular Hormones Therapy

*U S Marine Hospital, Brighton, Massachusetts*

- July 19 Diagnosis and Medical Treatment of Gastric Lesions Surgical Treatment of Gastric Lesions  
 August 16 Skull Fractures Injuries to Spine

*Station Hospital, Westover Field, Chicopee Falls, Massachusetts*

- July 19 Recent Advances in the Treatment of Mental Diseases and Management of Psychoneuroses  
 August 16 Thrombophlebitis and Emboli Vascular Surgery

*Dispensary, U S Naval Construction Training Center, Davisville, Rhode Island*

- July 19 Burns and Reconstruction Surgery  
 August 16 Blood Dyscrasias

*U S Naval Hospital, Newport, Rhode Island*

- July 19 Thyroid, Pituitary and Adrenal Diseases Ovarian and Testicular Hormone Therapy  
 August 16 Burns and Reconstruction Surgery

*Station Hospital, Bradley Field, Windsor Locks, Connecticut*

- July 19 Arterial Disease Inflammatory Arterial Disease  
 August 16 Diagnosis and Medical Treatment of Gastric Lesions Surgical Treatment of Gastric Lesions

*U S Naval Submarine Base, New London, Connecticut*

- July 19 Contagious Diseases and Complications  
 August 16 The Use of Penicillin and Sulfa Drugs

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman, Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M Baker, Dr E R Schmidt Dr E L Sevringhaus, Dr F D Murphy

*Gardner General Hospital, Chicago, Illinois*

- July 18 Bone and Joint Infections  
 July 25 Arterial Vascular Disease—Traumatic Lesions

*Station Hospital, Fort Sheridan, Illinois*

- July 18 Repair of Bone in Fractures and Diseases

*Vaughan General Hospital, Hines, Illinois*

- July 18 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment  
 July 25 Conditions Affecting Glucose Metabolism

*Mayo General Hospital, Galesburg, Illinois*

- July 18 Blood Dyscrasias, Malaria, Filariasis  
 July 25 High Blood Pressure

*Station Hospital, Chanute Field, Illinois*

- July 18 Mental Hygiene and the Prevention of Neuroses in War  
 July 25 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases

*Station Hospital, Camp McCoy, Wisconsin*

- July 18 Plexus and Peripheral Nerve Injuries  
 July 25 Dermatological Diseases

*Station Hospital, Triana Field, Wisconsin*

- July 18 Endocrinology  
 July 25 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment

*Billings General Hospital, Indiana*

- July 18 Peptic Ulcer, Gall Bladder and Liver Diseases  
 July 25 Low Back Pain

*Wakeman General Hospital, Camp Atterbury, Indiana*

- July 18 Chest Diseases and Diseases of the Larynx  
 July 25 Bone and Joint Infections

REGION No 23 (Nevada, Northern California)—Dr S. R. Mettler, Chairman, Dr E. H. Falconer, Dr D. N. Richards

*Dibble General Hospital, Menlo Park, California*

- August 6 Coronary Diseases Diagnosis and Management—Dr Edwin L. Bruck  
 Rheumatic Fever—Lieutenant Maurice Sokolow

REGION No 24 (Southern California)—Lt Comdr Geo. C. Griffith, Chairman, Capt H. P. Schenck, Dr J. F. Churchill, Dr W. A. Morrison, Maj N. Nixon

*Birmingham General Hospital, Van Nuys, California*

- July 25 Surgery of the Traumatic Urinary Tract—Lieutenant Commander Carl Rusche

*A A F Regional Hospital, March Field, Riverside, California*

- July 17 Communicable Disease—Major Norman Nixon and Captain Charles D. Marple

*Station Hospital, Camp Cooke, Lompoc, California*

- July 18 Plastic Surgery in Defects of the Head and Neck—Dr Edward Lamont

*U S Naval Air Training Station, San Diego, California*

- July 20 Classification and Diagnosis of Anemias—Dr Alvin Foord

*Hoff General Hospital, Santa Barbara, California*

- July 18 Plastic Surgery in Defects of the Head and Neck—Dr Edward Lamont

*A A F Regional and Convalescent Hospital, Santa Ana Army Air Base, California*

July 17 Wound Healing—Major Walter Birnbaum

*U S Naval Hospital, Santa Margarita Ranch, Occanside, California*

July 26 Management of the Diabetic Patient—Dr John Sherrill

*U S Naval Hospital, Long Beach, California*

July 18 Penicillin in Syphilis and Gonococcic Infections—Lieutenant Commander W Duemling

*U S Naval Hospital, Corona, California*

July 26 Thyroid Disease—Lieutenant Commander George Crile, Jr

LETTER TO THE AMERICAN COLLEGE OF PHYSICIANS FROM

MAJOR JAMES G BRUCE, (MC), U S ARMY

(ASSOCIATE OF THE AMERICAN COLLEGE OF PHYSICIANS),

RECENTLY LIBERATED FROM BILIBID PRISON, MANILA

"On May 1, 1941, my initial active duty was at Fort Ethan Allen, Vermont, where I was Chief of the Medical Service and Acting Commanding Officer for a short period. Duty in this country was short-lived and I sailed for Manila on August 9, 1941. There I was assigned to the Sternberg General Hospital and became Head of the General Medical Section under Major J O Gillespie, F A C P, who was the Chief of the Medical Service. Major Gillespie later commanded another hospital on Bataan, at which time he became a full Colonel. After we were captured by the Japanese, he, being a Colonel, was taken immediately to Formosa with the other Colonels and Generals.

"After Pearl Harbor, our general medical wards at Sternberg were converted to surgical wards in order to cope with large numbers of bombing casualties. From December 12 to December 25 I was Executive Officer of one of the annexes of Sternberg General Hospital. We had only ten Filipino doctors and practically all Filipino help. We had 300 beds designated to take medical cases only, all surgical and casualty cases were to go to Sternberg or some other annex. This also was short-lived. The Japanese were nearing Manila. On December 25 orders came to evacuate the patients, beds, medical supplies and equipment to Bataan. We sailed for Bataan on Christmas night.

"On Bataan I was assigned to General Hospital No 1, designated as Chief of the Medical Service, carrying on also one medical ward. The medical service was light, but we were short of doctors. On January 25, 1942 this hospital was moved to the rear and I was transferred to General Hospital No 2. Here, unlike Hospital No 1, there were no buildings, our patients occupied beds in the jungle, right out in the open. I had a minor surgical ward and was kept busy amply. From this time until the fall of Bataan, malaria and dysentery rose in incidence and almost every casualty needed medical treatment to supplement the care of his battle wound.

"At the fall of Bataan on April 9, 1942, we were ordered by the Japanese to keep on in the treatment of our hospital cases. They did not touch the medical or pharmacy supplies but to our dismay they hauled away all of our food supplies, except rice. They also surrounded our hospital area with artillery batteries and began firing on Corregidor. Our counter batteries from Corregidor were accurate and only one shell fell in the hospital area and the casualties were few.

"The Japanese closed this hospital on May 26, 1942 (everyone was cured by edict) and our hospital personnel was sent to Cabanatuan (via a four-day stopover in Bilibid Prison at Manila) At Cabanatuan, Prison Camp No 1, we established a hospital as best we could, using the medicine and instruments we had carried in on our backs By this time, Americans at this camp were dying at the rate of fifteen to fifty per day, water was scarce, food consisted of rice and a thin vegetable soup, sanitation was nil and the rainy season was on About all we could do was to identify the dead and reassure the living

"Later, in 1943, our slant-eyed hosts decided to give us a livable diet with fresh meat and brought in a few critical items such as quinine, aspirin, emetin, and gave us a microscope to use The boys ceased to die, but we had lost 2,600 in the first six months of camp

"I was most fortunate to remain as a ward officer in this hospital throughout 1943 and most of 1944 There was a diphtheria epidemic, which subsided spontaneously The Japanese finally furnished us with antitoxin in sufficient quantities, just as the epidemic was subsiding It is interesting to note there were cases involving the larynx, conjunctiva, penis, and several cases were followed by paralyses Our dysentery area at one time in late 1943 contained 1200 cases with positive stools for ameba Ninety per cent of all patients at one time or another presented symptoms and signs of at least one vitamin deficiency such as xerophthalmia with corneal ulcer, beriberi in all its forms, massive edema, scurvy, ariboflavinosis or pellagra It is regrettable that research work could not be carried out on this abundance of clinical material, but it was impossible with no laboratory (except a microscope and two pipettes), with little or no medicine, especially vitamins, and no paper to work with except the backs of milk can labels and cigarette packages, which were used for clinical records

"In January of 1944, the Japanese told us that since we had Red Cross food packages (the Gripsholm also brought drugs, shoes, toilet articles and other items) they would stop our killing carabao for fresh meat They reduced the rice ration from 550 grams per day to 400 grams per day This was only the first cut Later it went to 300 grams, then 200 grams per day, and when the Yanks came in, the diet was at 150 grams per man per day Everyone began to lose weight Items which previously could be purchased in the commissary became unobtainable or out of reach in price due to inflation (officers were paid in Japanese script or invasion money, which we called Mickey Mouse money) Patients who had overcome their vitamin deficiencies in 1943 now were again burdened with beriberi and pellagra Many of us started little gardens of our own, but the only vegetables that could be raised on the soil of that area without fertilization were okra and egg plant

"On September 21, 1944, I had the biggest thrill of my life American planes flew over, a beautiful sight, not just a few like the Japs fly, but literally hundreds of them, looking like a great flock of geese On returning from their mission, two planes left formation, flew low over camp, dipped their wings and cleared their guns At last Americans had returned after more than two years of waiting! From that time on we saw many planes Our guards were quite disgusted We always went out to see them, but the Japs dove into their previously prepared foxholes and forgot about their sentry posts, even if the flight was miles away

"In October, 1944, I was fortunate to be picked by the Japanese to join a detail of ten medical officers and sixty-five corpsmen destined for Bilibid Prison in Manila to take over the hospital there A similar detail was picked to remain at Cabanatuan and the excess of the medical personnel from both places was evacuated to Japan with the 'healthy' (so-called by the Japs) prisoners

"Bilibid Prison, built by the Spanish, made livable by the Americans in the early 1900's, is the place where Walker did his famous work on amebae, differentiating

histolytica from coli, using convicts for clinical material. It is not a pleasant place, being surrounded by thick stone walls twenty-five feet high, but to us it afforded running water in plenty from the Manila city supply and automatic flush straddle trenches, the latter built in 1942 by the ingenuity of American prisoners of war. Sanitation was no longer a problem.

"The real problem at Bilibid, however, was food. The Japs claimed it was hard to get food into Manila because of lack of transportation. Whatever the reason, we did not get it and the patients suffered. A diet of 1,000 calories—150 grams of rice, 50 grams of cornmeal and 50 grams of soy beans, was not enough. It not only was unbalanced, but lacked vitamins, it was difficult for a dysentery case to digest. Wood also was rationed and, coupled with lack of cooking facilities in the kitchen, it was impossible to get out more than two meals per day. Our mess officer inveigled some canned milk from the Japs, which was used up a few weeks before the Yanks came in. This milk was used on the severe malnutrition cases. Many patients lacked clothes, blankets and bedding. There were beds only for those who were critically ill. The remainder lay on mattresses, or nothing at all on the concrete floor.

"Each medical officer at Bilibid had an administrative job, as well as professional duties. I was Executive Officer and Registrar, besides having one ward and being Chief of the Medical Service. Fortunately, we were all in good condition when we left Cabanatuan and our stay at Bilibid was interrupted by General MacArthur and his troops.

"On February 4 of 1945 the Jap guards left the compound at 1:30 p.m., leaving a note in English stating that we were free, but that we should not leave the compound and that they, the Japanese, were called on another mission. Five hours later there was a tap on a boarded-up window in one of the outside walls. Our patients tore down the boards and there they were, face to face with a group of American soldiers and their officers. A yell went up like that after the winning touchdown at a football game! We could not believe we were back under the American flag, but good old American food, with plenty of coffee, sugar, milk and butter soon convinced us.

Sincerely yours,

JAMES G. BRUCE, Major, (MC), U. S. Army  
(formerly Springfield, Mass.)

(Editor's Note: Dr. Bruce during his imprisonment was a Captain. He has been promoted to Major as of February 23, 1945, and according to recent press releases has been voted the Legion of Merit from General MacArthur. He has regained his strength and also thirty-five pounds in weight, lost while in Bilibid Prison. He reported to the Lovell General Hospital, Fort Devens, Mass., on April 22 for medical observation and on May 3 was released on thirty days sick leave. He will report back to Lovell General Hospital on June 7, following which he will probably receive sixty days regular leave. In late August he will be reassigned to duty. Two other members of the College, Lieutenant Commander William M. Siliphant, (MC), U. S. Navy, and Lieutenant Commander J. LaMonte Zundell, (MC), U. S. Navy, also liberated from Bilibid Prison, were patients of Major Bruce at time of liberation.)

## OBITUARY

## DR CHARLES HENRY LAWRENCE

Dr Charles Henry Lawrence of Boston, Fellow of the College, died on March 13, 1945, following a coronary artery thrombosis. He was born on October 17, 1882, in Chicago. Following his precollegiate training in Illinois, he entered Harvard College and was graduated in 1904, although he had earned his A B *cum laude* a year earlier. In 1908, he was granted the degree of M D from the Harvard Medical School, and then served as a house officer at the Massachusetts General Hospital. From 1911 to 1917, he held various appointments at the Massachusetts General Hospital and the Harvard Medical School. During World War I he served as a First Lieutenant in the Medical Corps, U S Army, and following the war he was appointed physician at the Evans Memorial Hospital of the Massachusetts Memorial Hospitals, a position which he held with distinction until 1934 when he became Chief of the Endocrine Clinic of the Boston Dispensary and attending physician at the New England Medical Center. From 1934 until 1945, he was also an instructor and assistant professor of medicine at Tufts Medical School.

In 1911, Dr Lawrence married Muriam Oliver Williams of Plymouth, Massachusetts. They had four sons, Charles Henry 3rd, Edward Williams, David Bissell, and George Hugh.

At the time of his death Dr Lawrence held the following positions: assistant professor of medicine, Tufts College Medical School, physician-in-chief of the Endocrine Clinic and consulting physician of the Children's Clinic, New England Medical Center, member of Associate Staff, Faulkner Hospital, consulting physician, Charles Choate Memorial (Woburn) and Symmes Arlington Hospitals, consultant in endocrinology, Joseph H. Pratt Diagnostic Hospital. He was a member of the following societies: Massachusetts Medical Society, Society for the Study of Internal Secretions, and American Clinical and Climatological Association, Aesculapian Club, Fellow, American Medical Association, and Fellow, American College of Physicians since 1929.

His friends and associates had a high regard for his professional ability and character. Aside from his profession he was interested in music, religion, and sailing.

No greater tribute can be made than a quotation from one of his close friends and colleagues: "I can testify that for intellectual honesty, devotion to the good of his fellowmen, broad, understanding charity of outlook towards all, and complete selflessness he stands out as a real, practising Christian gentleman."

All men who knew Dr Lawrence will miss him as a loyal friend, an excellent doctor and clinical investigator.

CHESTER S. KEELER, M D, F A C P,  
Governor for Massachusetts

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## PENICILLIN IN SUPPURATIVE DISEASE OF THE LUNGS DUE TO *STREPTOCOCCUS* *HEMOLYTICUS*\*

By HAROLD J F KULLMAN, Commander, MC, USNR, FACP, and  
JACOB ANTRIM CRELLIN, Lieutenant Commander, MC,  
USNR, FACP

SINCE penicillin has been employed clinically only since 1941 and, until comparatively recently, has not been available in sufficient quantity to permit the study of a large series of cases, the amount of literature concerning its clinical use in suppurative diseases of the lungs is necessarily limited. There is now sufficient evidence, however, to justify its employment in pneumonia, suppurative pneumonitis, lung abscess and empyema when due to an organism or organisms susceptible to the antibiotic action of penicillin.

Although a definite decrease of empyema has occurred since the use of the sulfonamides, there is a limited group of sulfonamide resistant cases who develop empyema during the course of their treatment. Then, too, empyema may already have been present when sulfonamide was started. Tillett, Cambier and McCormack<sup>3</sup> found bacteria retained viability in the pleural space after sulfadiazine was injected intrapleurally. They also demonstrated the cure of empyema without rib resection when penicillin was placed directly into the empyemic cavity. Blake and Craige<sup>4</sup> report the successful use of penicillin in three cases of suppurative disease of the lung, due to staphylococcus in two cases and *Streptococcus hemolyticus* in the third.

Penicillin was used successfully in sulfonamide-resistant pneumonia by Bennett and Parkes<sup>5</sup>. They state that the results obtained in their cases represent a new phase in the treatment of empyema. Here, again, thoracotomy was obviated.

When penicillin is injected intravenously or intramuscularly, it does not penetrate in significant amounts into walled-off collections of pus such as may be found in thoracic empyema or an abscess cavity. Conversely, penicillin injected directly into an abscess does not escape rapidly.<sup>1, 2</sup>

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\* Received for publication November 20, 1944



One of the most remarkable properties of penicillin is its capacity to act in the presence of large quantities of pus and bacteria. On the other hand, we know that there are inhibitory substances in pus that prevent the action of sulfonamides. The use of penicillin intrapleurally may, therefore, prove revolutionary in the treatment of empyema and related pulmonary suppurative disease. This will probably be true not only in sulfonamide-resistant cases but in all cases in which the causative invading organism is susceptible to the action of penicillin.

## PENICILLIN

|          | Diagnosis   | Total Dosage | Days of Treatment | Pleural Injections | Days on Sick List |
|----------|---|--------------|-------------------|--------------------|-------------------|
| Case I   | Pneumonia, <i>Streptococcus hemolyticus</i><br>Abscess, Pulmonary, R L L                      | 3,020,000 U  | 24                | 0                  | 172               |
| Case II  | Pneumonia, <i>Streptococcus hemolyticus</i><br>Abscess, Pulmonary, R U L                      | 1,475,000 U  | 14                | 0                  | 143               |
| Case III | Pneumonia, <i>Streptococcus hemolyticus</i><br>Pleuritis, Suppurative, Left                   | 1,010,000 U  | 8                 | 8                  | 146               |
| Case IV  | Scarlet Fever,<br>Pneumonia, <i>Streptococcus hemolyticus</i><br>Pleuritis, Suppurative, Left | 1,300,000 U  | 11                | 5                  | 125               |
| Case V   | Pneumonia, <i>Strep hemolyticus</i> , Multiple Lobe<br>Pleuritis, Suppurative, Left           | 2,140,000 U  | 15                | 15                 | 146               |
| Case VI  | Pneumonia, <i>Streptococcus hemolyticus</i><br>Pleuritis, Suppurative, Left                   | 400,000 U    | 8                 | 10                 | 151               |

Hemolytic streptococcal infections respond dramatically to penicillin. However, no large number has been treated, since most of them are susceptible to sulfonamide therapy.

We report here the treatment of six cases of suppurative disease of the lungs due to the *Streptococcus hemolyticus*. Two are cases of sulfonamide resistant lung abscess following hemolytic streptococcal pneumonia. The abscesses were located in the right lower lobe (case 1) and in the right upper lobe (case 2), in case 1 there was also multiple lobe spread due to the same organism. The other four are cases of empyema following hemolytic streptococcal pneumonia, in which the hemolytic streptococcus was isolated from the pleural fluid. Two of the empyema cases were sulfonamide-resistant and the other two were in such desperate condition that the sulfonamide did not receive a fair trial preceding the change to penicillin—one has only to witness the recovery of moribund patients such as these latter to realize that we now have a drug capable of performing what a few years ago would have been termed a miracle. A predominant growth of *Streptococcus hemolyticus* in the sputum was found in all cases during the course of the pneumonia and, in cases 1 and 2, at the time the lung abscesses were

active Cultures of the pleural fluid were positive for the same organism in the four empyema cases

The cases of lung abscess were successfully treated with penicillin given intravenously at first, followed later by 15,000 units intramuscularly every three hours and every four hours, respectively

In case 1 a total of 3,020,000 units was used over a period of 24 days and, in case 2 a total of 1,475,000 units over a period of 14 days The sputum became negative for hemolytic streptococcus in cases 1 and 2 in three days and two days, respectively, after the institution of penicillin, and com-

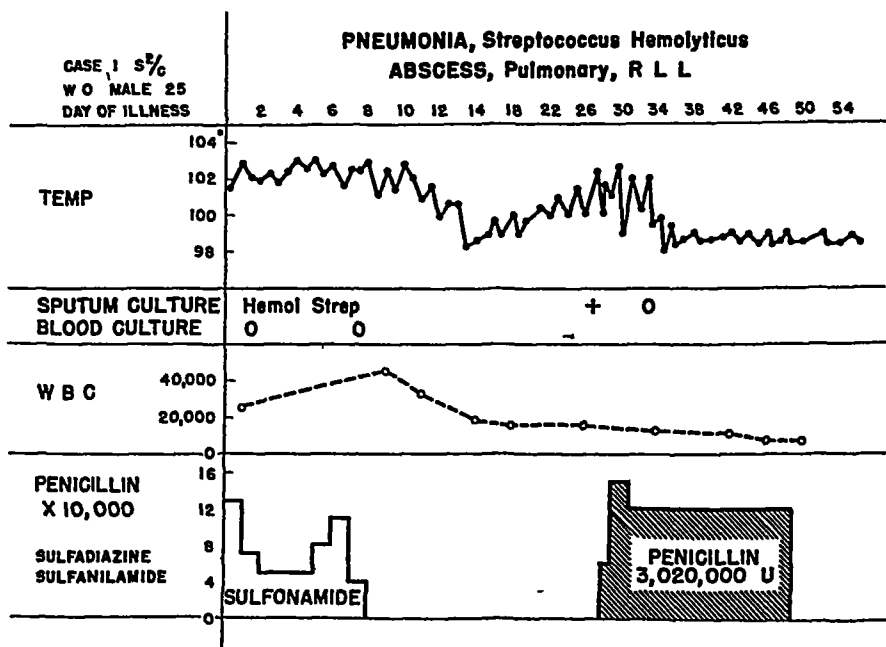


FIG 1 Case 1, clinical record

plete healing was demonstrated by roentgenogram in 26 and 34 days respectively Success was probably due to the fact that these abscesses were acute and thin walled

In the treatment of the four cases of hemolytic streptococcal empyema, intrapleural injections of 40,000 units of penicillin in normal saline solution were carried out every 12 hours during the critical stage and daily thereafter It is true that the number of treatments given intrapleurally appears high as compared with those reported by Tillett, Cambier and McCormack,<sup>3</sup> who recommend 30,000-40,000 units intrapleurally on alternate days with a minimum total of three treatments However, in view of the fact that one of eight cases they reported had recurrence and required thoracotomy, it would appear that more adequate dosage should be used

Pleural fluid cultures were negative after the first 24 to 36 hours in all of our cases of empyema except case 6, which had 10 intrapleural injections of 40,000 units of penicillin unsupported by intravenous or intramuscular penicillin In this instance the pleural fluid did not become negative on cul-

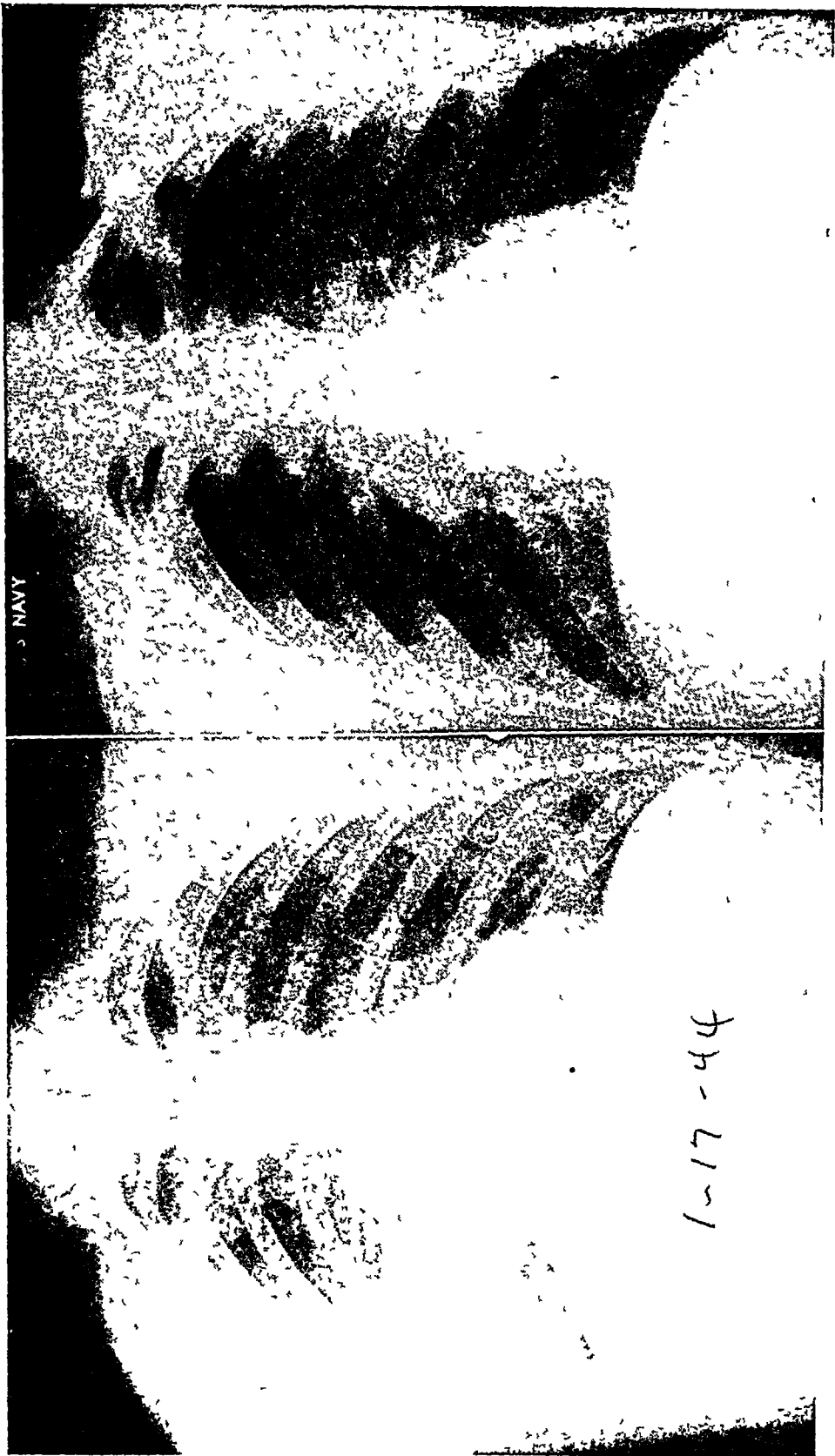


FIG 2 (Left) Case 1, before penicillin therapy  
FIG 3 (Right) Case 1, final roentgenogram

ture until the sixth day, which suggests that the primary focus in the neighboring lung tissue had not been affected by the penicillin in the pleural space

It is interesting to note that, in one of our sulfonamide-resistant cases, there was present a pleural fluid concentration of 9 mg per cent of sulfonamide before changing to penicillin therapy, yet the pleural fluid was positive for hemolytic streptococcus on culture

Our findings and results in this small number of cases seem to indicate that supportive systemic penicillin treatment, in addition to intrapleural injections, should be given in cases of empyema due to hemolytic streptococcus infection

#### CASE REPORTS

*Case 1* W O, male, age 25 The onset of this seaman's illness occurred 36 hours prior to admission with generalized aching, followed 12 hours later by chilliness, pain in right chest and non-productive cough Blood culture on admission was negative Roentgenographic examination showed evidence of consolidation in the right lower lobe and irregular patchy infiltration in the left lower lobe Continuous oxygen therapy was necessary, as cyanosis developed when he was removed from the tent The sputum showed a predominant growth of *Streptococcus hemolyticus* Fifty-eight grams of sulfadiazine and sulfanilamide over a period of eight days had little effect The white blood cell count varied from 24,500 on admission to 44,000 when sulfonamide was stopped Following some clearing of the pneumonic process, a roentgenogram showed evidence of an abscess located at the apex of the right lower lobe, with a definite fluid level at the seventh rib posteriorly On the twenty-seventh day following admission penicillin therapy was begun Continuous intravenous drip was used during the first 24 hours, followed by 15,000 units every three hours intramuscularly

The temperature, white blood cell count, and size of the cavity were steadily reduced, with rapid improvement in the general condition of the patient

*Result* There was complete healing of the abscess cavity in this sulfonamide resistant case of hemolytic streptococcal infection

Total amount of penicillin, 3,020,000 units

*Roentgen-ray* A fine fibrous strand was demonstrable in the region of original cavity

The patient returned to a full duty status in 172 days, which included convalescent care and light duty before discharge from hospital

*Diagnosis* Pneumonia, lobar, multiple lobe, abscess, pulmonary, right lower lobe, *Streptococcus hemolyticus*

*Case 2* D L, male, age 21 This 21 year old seaman was admitted to the hospital on December 19, 1943 His present illness began one week prior to admission with a sore throat, followed by malaise and generalized aching He became progressively worse and 24 hours prior to admission had nausea, vomiting and chills Physical examination revealed a temperature of 105° F, pulse of 120 and respirations 34, and the roentgenogram revealed consolidation of the right upper lung field He appeared acutely ill but had little pulmonary embarrassment, and he responded slowly to sodium sulfadiazine and sulfanilamide His temperature reached normal on the tenth day and then began spiking daily to 102° F, with pain on coughing over right upper anterior chest On January 3, 1944, the roentgenogram revealed some clearing centrally but also a small rounded area of increased radiolucency at the third anterior interspace, which was somewhat suggestive but not diagnostic of abscess cavity Repeated sputum examinations continued to show *Streptococcus hemolyticus* predominant on culture By January 5, 1944 his temperature reached 104° F, and

respirations were 26 White blood cell count again rose to 16,000 with 84 per cent polymorphonuclears On January 5, 1944, penicillin therapy was begun, 5,000 units being given every hour by the intravenous route This was followed by 15,000 units intramuscularly every four hours day and night, with a total dosage of 2,140,000 units of penicillin over a period of 14 days On the day penicillin therapy was started, a roentgenogram of the chest showed that the area of increased radiolucency appeared larger than when first noted, measuring 3 cm in diameter, with a fluid level Four days after the institution of penicillin therapy, temperature reached normal and remained so except for slight spiking to 99.6° F The sputum, which had been repeatedly positive for *Streptococcus hemolyticus*, became negative in 48 hours after the institution of penicillin and remained negative thereafter Recovery was rapid, and on April 10, 1944, roentgenogram showed only a minimal amount of residual infiltration in the area of the former abscess The patient returned to a full duty status on April 12, 1944 A roentgenogram after return to duty showed only a small fibrous strand in the area of the former abscess

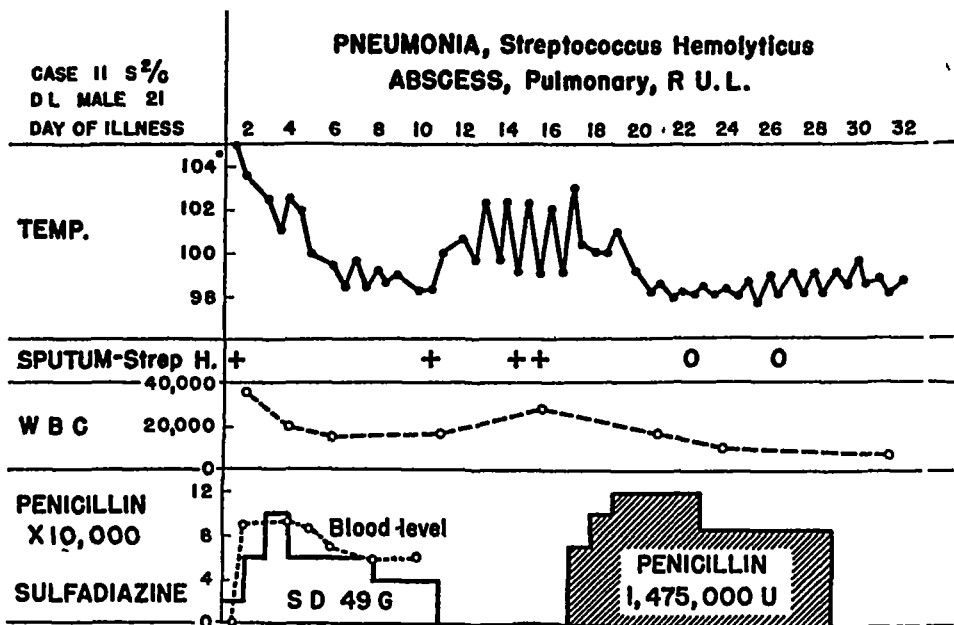


FIG 4 Case 2, clinical record.

**Résumé** This is a sulfonamide-resistant case of pneumonia, lobar, *Streptococcus hemolyticus*, showing repeatedly positive sputum cultures until 48 hours after penicillin therapy was instituted The abscess which developed in the right upper lobe apparently was sufficiently thin walled to have absorbed the drug

Total dosage 1,475,000 units over a period of 14 days

The patient returned to full duty status in 143 days

**Diagnosis** Pneumonia, lobar, right upper lobe, abscess, pulmonary, *Streptococcus hemolyticus*

**Case 3** W M, male, age 19 This patient was admitted with complaint of pain in left chest of two days' duration, requiring a hypodermic for relief while in the dispensary He had a severe cough but no hemoptysis

Temperature was 102–103° F, white blood cells numbered 34,000 and the sputum showed predominating growth of *Streptococcus hemolyticus* After 59 grams of sulfadiazine over a period of six days, this case was considered to be sulfonamide-resistant The patient continued to run a septic temperature, with a leukocytosis of 16,900, and signs of fluid were present over the left lower chest Aspiration revealed

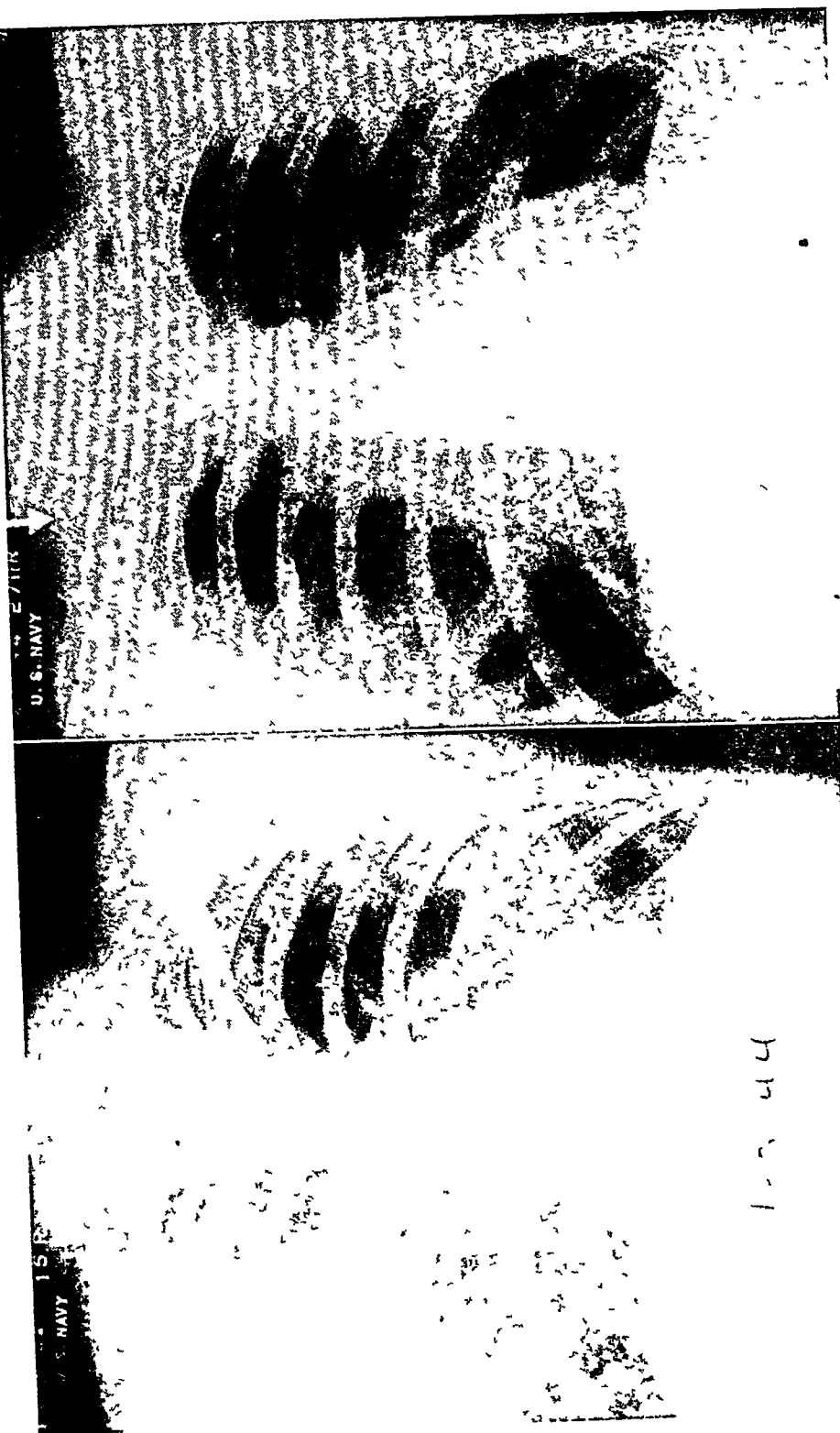


FIG 5 (Left) Case 2, roentgenogram before penicillin therapy and after 49 grams of sulfonamide  
 FIG 6 (Right) Case 2, final roentgenogram

240 c.c. of cloudy pleural fluid. The culture was positive for *Streptococcus hemolyticus* in 24 hours and penicillin therapy was begun.

A total of 1,010,000 units of penicillin was given over a period of eight days. 320,000 units (eight injections of 40,000 units each) were injected into the intrapleural space within six days, and the remaining 690,000 units were given by intramuscular injections of 15,000 units every four hours day and night for eight days.

The patient returned to full duty status in 145 days. There was no residual pleuritis or fibrosis, and thoracotomy was obviated.

**Diagnosis** Pneumonia, lobar, *Streptococcus hemolyticus*, pleuritis, suppurative, acute, *Streptococcus hemolyticus*.

**Case 4** P D, male, age 19. This patient was admitted to the hospital 10 days after the onset of an acute upper respiratory infection, for which he spent seven days in the sick-bay of the dispensary. On the day of admission to the hospital he developed severe headache, chill, vomiting and a temperature of 103° F. A diffuse erythematous rash and typical scarlatinal throat findings were present. His condition grew rapidly worse, with delirium, restlessness, temperature of 105° F, pulse 150, respirations 40, and findings of consolidation in his left lower lobe. Sodium sulfadiazine intravenously and sulfadiazine by mouth resulted in no change in the patient's condition in the first 24 hours. Signs of fluid were present at this time, and aspiration revealed cloudy seropurulent fluid which on culture showed an abundant growth of *Streptococcus hemolyticus*.

Daily tap and instillation of 40,000 units of penicillin for five doses was supported by 5,000 units hourly by intravenous route for 24 hours, followed by 15,000 units intramuscularly every four hours day and night. A dry tap was obtained on the eighth day.

**Résumé** Sulfonamide therapy at the outset was insufficient to demonstrate this case sulfonamide-resistant.

A total of 1,300,000 units of penicillin was given over a period of eight days, of which 200,000 units were injected intrapleurally. Thoracotomy was obviated in this case.

The patient returned to full duty status in 125 days, and check-up roentgenograms taken after return to duty showed no evidence of residual pleuritis or fibrosis.

**Diagnosis** Scarlet fever and pneumonia, lobar, pleuritis, suppurative, *Streptococcus hemolyticus*.

**Case 5** D P, male, age 18. The onset of this seaman's illness occurred three days prior to admission while he was en route from a coastal station. Cough and severe left chest pain were present, with temperature of 105° F, leukocytosis of 42,000 with 87 per cent polymorphonuclear cells. *Streptococcus hemolyticus* was the predominant organism in the sputum and blood culture was sterile.

Following sodium sulfadiazine given intravenously and sulfadiazine orally, continuous oxygen and supportive measures, his condition was considerably worse. On the second day, cloudy fluid was aspirated from the left pleural space and found positive on culture for *Streptococcus hemolyticus*, whereupon there was started continuous intravenous penicillin in normal saline solution. In addition, three aspirations of pleural fluid and instillations of penicillin were performed during the following 24 hours, 40,000 units being injected following each aspiration. The next day two aspirations were done, each followed by injection of 40,000 units. Culture of fluid and direct smear 24 hours after starting this treatment were negative for organisms. Subsequently, cultures of the pleural fluid aspirated remained sterile. Sputum cultures remained positive and intramuscular treatment with penicillin, in support of the intrapleural treatment, was given following discontinuance of the intravenous penicillin. The pneumonic process in the right upper and middle lobes cleared quickly, but residual findings of fluid in the left pleural space necessitated a total of 15 aspirations and a similar number of penicillin instillations.

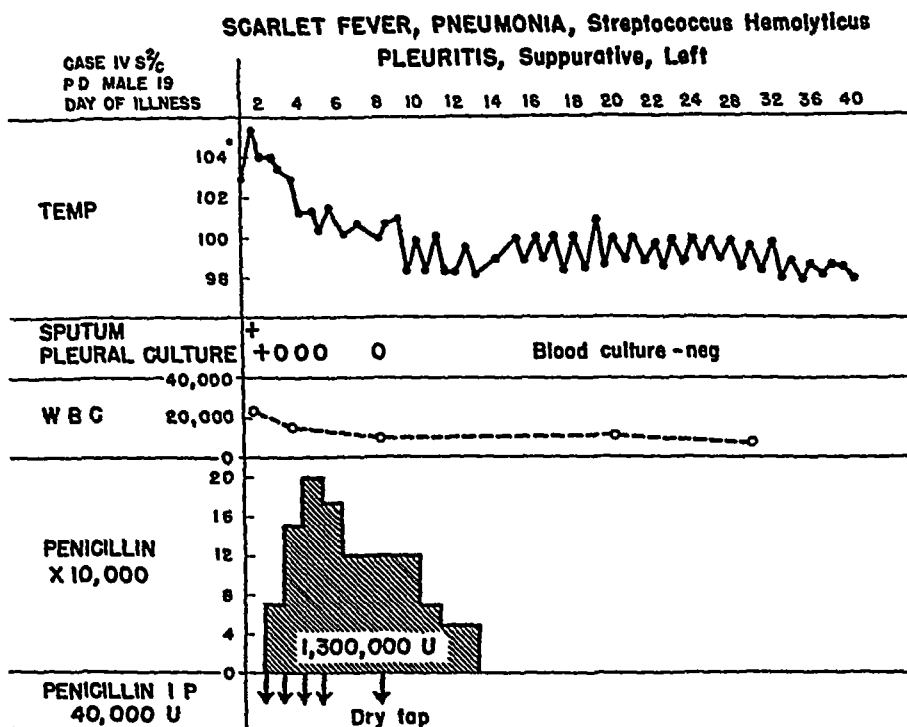
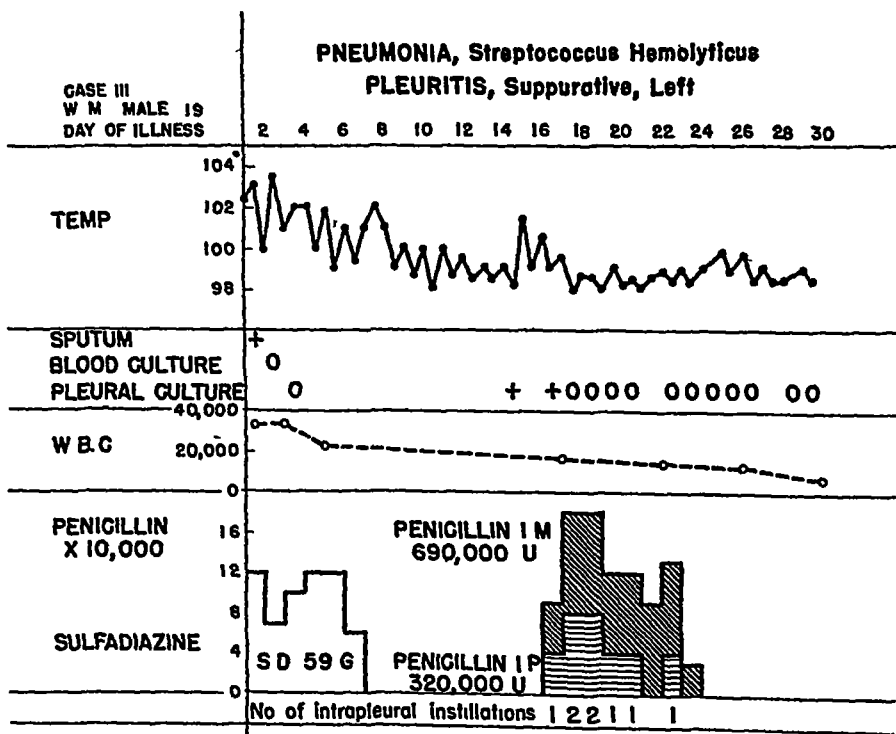


FIG 7 (Above) Case 3, clinical record

FIG 8 (Below) Case 4, clinical record



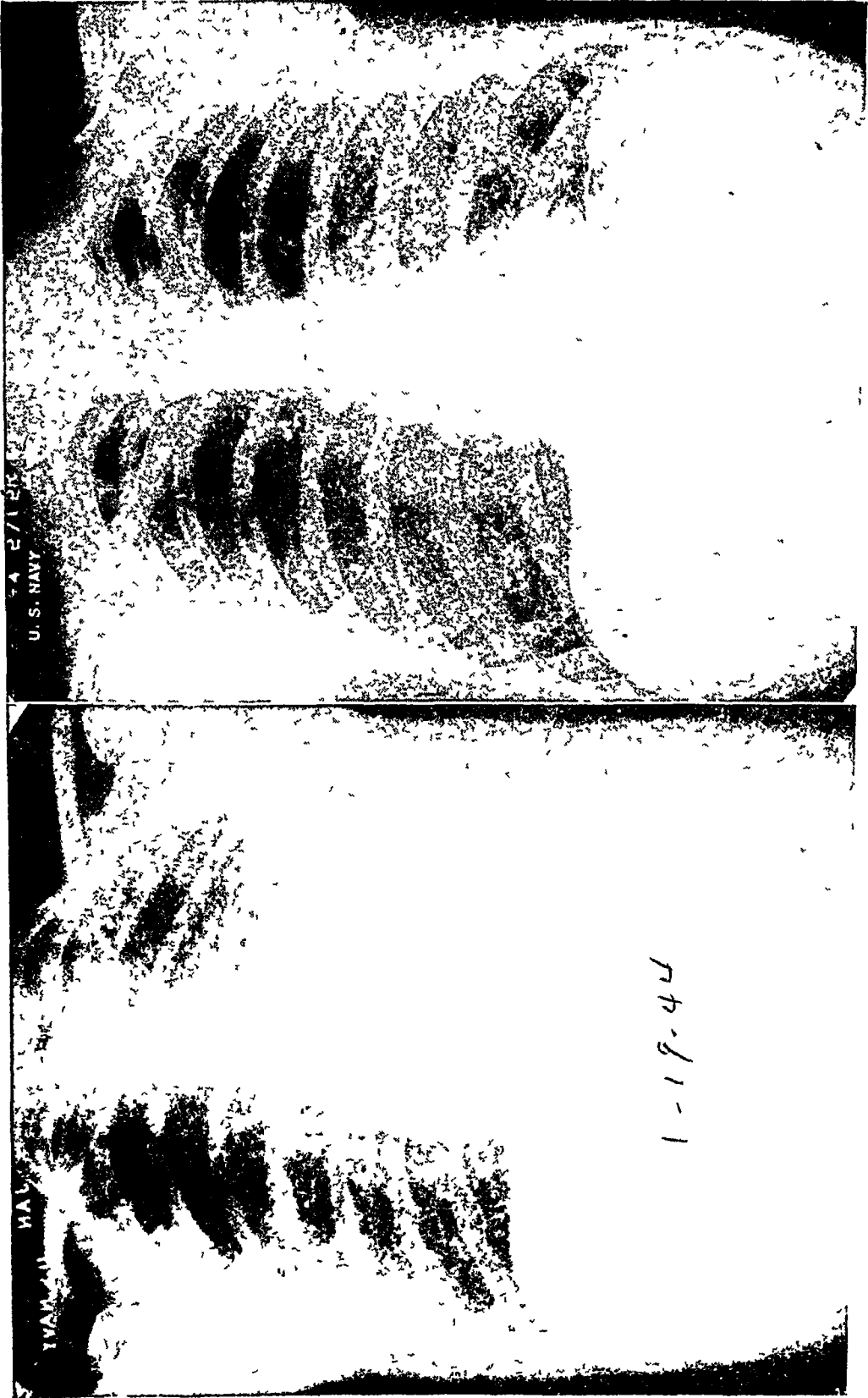


FIG 9 (Left) Case 4, roentgenogram taken during course of penicillin therapy  
FIG 10 (Right) Case 4, final roentgenogram

**Resumé** This patient returned to full duty status after 151 days on the sick list. Final roentgenogram on discharge from the hospital showed residual slight pleural thickening, diaphragmatic blunting and obliteration of the costophrenic sulcus.

A total of 2,140,000 units of penicillin was given, of which 600,000 units were injected intrapleurally in 15 doses of 40,000 units each.

Sulfonamide therapy at the outset was insufficient to demonstrate this case sulfonamide-resistant. The desperate condition on the second day warranted a change of treatment.

**Diagnosis** Pneumonia, lobar, multiple lobe, *Streptococcus hemolyticus*, and pleuritis, suppurative, acute, left.

**Case 6** F Z, male, age 19. The patient was admitted to the hospital with a history of cough, chill and knife-like pain in the left lower chest. Physical findings of consolidation were supported by roentgenographic findings of consolidation of the left lower lobe. The original roentgenogram showed narrowing of the intercostal spaces on the left with increased obliquity of the ribs on this side. Sputum culture before sulfonamide therapy showed predominant growth of *Streptococcus hemolyticus*. The blood culture was negative.

Past history showed repeated chest and upper respiratory infections from the age of four. At times these were followed by asthma.

Clinical course showed a poor response to intravenous sodium sulfadiazine followed by sulfadiazine orally. A total dosage of 86 grams of sulfonamide was given over a period of 17 days. Signs of fluid developed and on the first aspiration it was clear and negative on culture. Temperature and leukocytosis persisted, and the second aspiration was cloudy and showed a good growth of *Streptococcus hemolyticus*.

Penicillin therapy was given only by the intrapleural route. Daily aspiration with instillation of 40,000 units of penicillin was followed for a period of eight days, on two of these days, 80,000 units were given by injections 12 hours apart. The cultures of the pleural fluid remained positive for organisms for five days after daily instillations of penicillin intrapleurally. Temperature returned to normal the twenty-first day and remained so. A thin layer of pleural fluid was found on tapping after penicillin had been discontinued. This proved negative on culture.

**Résumé** Sulfonamide-resistant case of pneumonia, lobar, *Streptococcus hemolyticus*, and complicating pleuritis, suppurative. Four hundred thousand units of penicillin were given by 10 intrapleural instillations of 40,000 units.

The patient returned to a limited duty status in 151 days because of slight dyspnea on severe exertion. The initial roentgenogram suggests the possibility of previous lung parenchymal damage and fibrosis.

Penicillin given only intrapleurally failed to sterilize the pleural space until the sixth day. Other cases having supplemental intravenous and intramuscular penicillin therapy were never positive after 36 hours.

**Diagnosis** Pneumonia, lobar, *Streptococcus hemolyticus*, pleuritis, suppurative.

## CONCLUSIONS

1 Two cases of lung abscess resulting in the course of sulfonamide-resistant *Streptococcus hemolyticus* pneumonia were successfully treated with penicillin parenterally. The number of days of penicillin therapy, 14 and 24, and the total dosage of 1,475,000 and 3,020,000 units are indicative of absorption of penicillin through thin walled cavities when treated over a sufficient period of time.

2 The sputum in the two cases of lung abscess became negative for hemolytic streptococcus in three days and two days respectively. Complete

healing, demonstrated by roentgenogram, occurred in 26 and 34 days, respectively

3 Four cases of *Streptococcus hemolyticus* empyema were successfully treated by intrapleural injection of penicillin supported by intravenous and intramuscular use of the drug Two of these cases were classified as sulfonamide-resistant and the other two had insufficient sulfonamide to be classified as such The latter were moribund

4 Thoracotomy was obviated in all cases of empyema

5 No evidence of reinfection or recurrence has occurred in any of these cases

6 Aspirated pleural fluid remained sterile after 24 to 36 hours, when the intrapleural treatment was supplemented by intravenous and, later, by intramuscular penicillin The case receiving only intrapleural penicillin retained an infected pleural space until the sixth day after treatment was started Success or failure may hinge upon the supplemental parenteral administration of penicillin

7 Residual fibrosis and subjective slight dyspnea necessitated return to a limited duty status in one case This seaman had had repeated infections with periodic asthma since the age of four The three other cases returned to a full duty status in 125, 146 and 151 days, respectively

#### BIBLIOGRAPHY

- 1 FLEMING, A, FLOREY, H W, BODENHAM, D C, CUTLER, E C, HUDSON, R V, CHRISTIE, R V, JEFFREY, J B, FLOREY, M E, and ROBINSON, J N Discussion on penicillin, Proc Roy Soc Med, 1944, xxxvii, 101-112
- 2 RAMMELKAMP, C H, and KEEFER, C S The absorption, excretion and toxicity of penicillin administered by intrathecal injection, Am Jr Med Sci, 1943, ccv, 342-350
- 3 TILLET, W S, CAMBIER, M J, and McCORMACK, J E The treatment of lobar pneumonia and pneumococcal empyema with penicillin, Bull New York Acad Med, 1944, xx, 142-178
- 4 BLAKE, F G, and CRAIG, B, JR Penicillin in suppurative disease of the lungs, a report of 3 cases, Yale Jr Biol and Med, 1943, xv, 507-516
- 5 BFNNETT, I, and PARKES, T Penicillin in sulfonamide-resistant pneumonias with special reference to staphylococcal infection and empyema, Lancet, 1944, i, 305-306
- 6 Case Records of Massachusetts General Hospital, Case No 30031, New England Jr Med, 1944, ccxxx, 82-87
- 7 MALLORY, T B Case Records of Massachusetts General Hospital, Case No 29162, New England Jr Med, 1943, ccxxviii, 519-522
- 8 MELENEY, F L The difficulty in evaluating drug treatment in surgical infections, Jr Am Med Assoc, 1944, cxlii, 1021-1026

# UPPER RESPIRATORY INFECTIONS: A RÉSUMÉ OF RECENT PERTINENT DATA AND OBSERVATIONS OF INCIDENCE ABOARD A DESTROYER \*

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THE recent emphasis by many observers that upper respiratory infections constitute a very important cause of incapacitating man power prompted the present study aboard a destroyer. The comparative incidence of such infections at sea and in port or where there were other opportunities for contact formed an added feature of interest. As the scope of this subject matter is rather diverse, it seems pertinent primarily to review the varied component features.

## I GENERAL CONSIDERATIONS

The term "upper respiratory infections" is a thoroughly non-specific one and includes the common cold, catarrhal fever, influenza or "flu," acute pharyngitis, and tonsillitis. Although these various entities are quite unrelated as to etiology, they are similar in their epidemiology and pathology, and in the fact that together they form the most important factor in loss of time in industry and in the military services, as recently stressed by Keefer <sup>1</sup>

*A Statistics* In a survey of absenteeism in 11,446 munitions workers in England, Massey and Pearson <sup>2</sup> found that 50 per cent of all male workers and 45 per cent of all female workers lost some time due to illness (in a period of six months), colds and influenza resulted in 23.7 per cent of the sick absences among males and 24 per cent among females, the greatest time waste due to any single group of illnesses. In the United States Navy, Smiley <sup>3</sup> has pointed out that since 1881 the median rate for colds and sore throat has been 2,500 per 1,000 per year, and for more severe respiratory infections (influenza, etc.) 86.9 per 1,000 per year. At a west coast shore station during a period of four summer weeks, 130 of 7,500 individuals were sick enough with catarrhal fever to require bed rest <sup>4</sup>. It is clear then that the illnesses included in the term "upper respiratory infection" actually do constitute a definite group. As such, they assume importance by virtue of their prevalence and the fact that they are "saboteur No. 1" in producing time loss in industry and in the military services. For these reasons, it is felt that any observations, however insignificant, should be recorded in the hope of further building up the facts concerning this group and thereby eventually eliminating their effects on manpower.

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*B Diagnosis* Although it seems permissible to deal with these diseases as a group, they should nevertheless be sharply delineated in the diagnosis of individual cases. Since they are similar in many of their manifestations, differential diagnosis is indeed difficult, though not impossible as pointed out by the Naval Laboratory Research Unit No. 1,<sup>5</sup> by Smiley,<sup>8</sup> and by Keefer.<sup>1</sup> The clinical picture is probably most significant in making a correct diagnosis, although laboratory aids are at hand, such as the identification of etiological agent in some instances by culture or animal inoculation, immunological or serological reactions including cold agglutinations in atypical pneumonia and blood counts. The therapeutic response to sulfonamides may also empirically suggest a group entity. When all other means seem inconclusive, clinical course and reasoning by a process of elimination may help to clarify the problem of diagnosis. The important point is that all who handle these cases should realize that differentiation is possible and earnest efforts should be made to be accurate in diagnosing these conditions. Only in this way can the problems concerning them be further clarified.

*C Pathology* The pathological aspects of these infections have been clearly and concisely presented by Warren.<sup>6</sup> From his descriptions, it is seen that the pathological differences are largely ones of degree rather than kind, being more severe in some with the outpouring of exudates, and mild in others with only hyperemia, congestion, and edema. Mucosa, submucosa, and underlying connective tissue are involved by the severe, invasive processes, whereas only the mucosa is involved in the mildest infections. Such a sequence of the pathologic lesions is a very graphic indication of the well-established belief that the etiological agents of these infections gain entrance through the nose or mouth. They settle on the mucosa of the respiratory tract and, other factors not being unfavorable for them, they proceed to multiply and invade the local tissues reaching various depths in accordance with their virulence. Some etiological agents, as a type, are usually mild (that causing the common cold) whereas others are vigorous (various streptococci). From this fact, the pathological condition which they evoke does suggest them by its degree, though not infallibly, since there is indeed a wide range of degrees of reaction to any one of these agents. Their similarity pathologically appears further to justify the consideration of these infections as a group.

*D Complications* The possible complications and sequelae of this group are numerous and important, varying from peritonsillar abscess to pneumonia, septicemia, arthritis, meningitis and nephritis. When complications do occur, they far outstrip the primary infection in morbidity and in causing loss of time. These facts give further prominence to upper respiratory infections. Measures by which complications might be prevented are naturally brought to mind. Sulfonamides have been found to be of little efficacy in the treatment of catarrhal fever,<sup>4</sup> or of "simple respiratory tract infections."<sup>7</sup> However, their use both locally<sup>8,9</sup> and by mouth is often recommended for the prevention of complications, particularly sinusitis,

pneumonia, etc. Their usefulness in the treatment of these complications (pneumonia, meningitis, septicemia, etc.) is undisputed. However, as Keefer<sup>1</sup> points out, there are needed adequate and effective chemotherapeutic agents for the treatment of the primary infections. It appears doubtful that penicillin will serve this latter purpose.

## II ETIOLOGY AND EPIDEMIOLOGY

*A The Causative Agents* The types of agents involved in these diseases are varied. Some are viruses, as in the common cold and influenza, some are staphylococci or streptococci, *H influenzae* or pneumococci, others are ill-defined as in catarrhal fever.

*B Transmission* All of these agents are presumably transmitted by the respiratory route as a result of direct contact with the patient (droplet infection) or with a healthy carrier. That carriers do occur in this group is well known and widely accepted, particularly in reference to those infections caused by streptococci, staphylococci, and pneumococci. Occasionally, especially in the case of streptococcus, milk may form the vehicle. A recent survey by Silverthorne and Patterson<sup>10</sup> indicates a scarcity of carriers of *H influenzae*—only one child was positive out of 55 children and 62 adults checked by nasopharyngeal culture.

*C Immunology* The concept of healthy carriers implies that some persons have an immunity to the infections in question. The existence of immune bodies for streptococci, staphylococci, and pneumococci is well established. The immunological properties of the influenza virus are less clear but are being rapidly elucidated. In an investigation of an influenza epidemic in military camps in Australia, Burnet et al.<sup>11</sup> noted that patients showed a sharp rise in antibody titer against the current strain of influenza virus in two weeks following the illness, whereas blood samples taken during the first few days of illness were much lower in antibody than were samples from normal subjects. Similar rises in antibody titer following influenza infections have been reported by Eaton and Martin.<sup>12</sup> Subcutaneous vaccination with both active and formalinized influenza virus preparations have also resulted in increasing the antibody titer both in blood serum<sup>13</sup> and in nasal secretions.<sup>14</sup> The work of the personnel of the Naval Laboratory Research Unit No. 1<sup>15</sup> in this regard dealt with a group of about 10,000 vaccinated and 10,000 unvaccinated (control) individuals and should, therefore, be quite conclusive. Vaccination by intranasal inoculation with living attenuated influenza virus (both A and B strains) also produced a significant rise in antibody titer in most patients<sup>15, 16, 17</sup>. According to Burnet,<sup>16</sup> this rise was most marked among those with lower initial antibody levels. The simplicity of the intranasal route, demanding less manpower, material, and time, makes it particularly inviting and the results especially significant.

It is stated by Bodily and Eaton<sup>16</sup> that there exists only a limited amount of antibody-specificity for strains of influenza A infection and in persons

immunized with influenza A vaccine. They consider that wide variations exist in the specificity of immune response of human subjects to any given strain of influenza virus. The Naval Laboratory Research Unit No. 1<sup>18</sup> points out that, whereas these serological data are of interest, they do not necessarily prove that the development of antibodies implies existence of actual immunity against influenza. In view of the facts regarding this matter in other diseases, however, it is reasonable to assume that there is a direct proportion between immunity and antibody titer. By way of demonstrating the correctness of this assumption, Henle et al.<sup>19</sup> subjected a group of persons immunized with formalin-inactivated influenza vaccine and a group of untreated control individuals to inhalation of an active influenza virus. They found that the antibody level before inhalation and the degree of protection from infection were directly proportional, those with the lowest antibody titers developing a clinical form of influenza, those with the highest titers being unaffected by the inhalations.

The existence of an influenza receptolysin is commented upon editorially in the *Journal of the American Medical Association*<sup>20</sup>. The work of Hirst<sup>21</sup> on the absorption of influenza virus on cells of the respiratory tract is noteworthy in this regard.

The immunology of influenza is thus being clarified. With others (catarrhal fever, common cold) of the group of upper respiratory infections, the picture is less well-defined. Considerable work on "cold vaccines" has been reported. Most of this is in accord with the study of Siegel et al.<sup>22</sup> who found no significant differences with regard to incidence, severity, or complications of colds between 120 controls and 125 experimental subjects, when a trial of "oral cold vaccine" was made.

*D Vitamins* The part played by vitamins in relation to this group of infections seems entirely non-specific. A two year controlled study by Cowan, Diehl, and Baker<sup>23</sup> of 774 college students on adequate diets indicates that the daily administration of multivitamin capsules did not significantly decrease the incidence, duration, and severity of colds. On the other hand, the use of vitamin concentrates, particularly vitamin C,<sup>24</sup> is probably of value during and after these illnesses. Thus, vitamins are no more important in upper respiratory infections than they are in any other infectious process. If the diet is primarily adequate, nothing is gained by an excessive vitamin intake.

*E Meteorology and Added Factors* A very important consideration in the epidemiology of upper respiratory infections is the relationship of weather, climate, and other environmental and situational factors. That such a relationship does exist is indicated by the various peaks of incidence of common colds in the United States (in January and February, April and May, September and October). An article by Mills<sup>25</sup> dealing with the general effects of climate upon disease is of interest here. The relationship certainly would seem logical since all vitality factors must have their functional basis

in energy liberated from tissue combustion, and the tissue combustion level is directly influenced by climate. Laboratory studies by Mills have shown that ability to fight infection is definitely higher under conditions that facilitate body heat loss than where heat loss is difficult. Thus, antibody production after typhoid vaccine injection into rabbits is almost twice as great in animals kept at a lower temperature. Locke<sup>26</sup> also provided support for the idea that combustion level is an important factor in determining resistance to infection. He found that the ability of animals to survive pneumococcus infection (by inoculation) or of human beings to maintain freedom from respiratory infection was related to their rate of oxygen utilization.

In addition to the effect of temperature alone, the storminess of a season, atmospheric pressure changes, and sudden chilling of the body seem in some manner related to the initiation of the infectious disease attacks<sup>25</sup>. The upper respiratory infections are most closely involved in this type of climatic effect. Thus, the summer freedom from respiratory infection is attributable in very large part to the lessened storminess of that season and the greater freedom from sudden body chilling. In the United States, the increased mortality from respiratory infections from summer low to midwinter high is three times that in Australia, though the latitudes of the countries are similar. The unusually stormy winters with great atmospheric turbulence in the United States are held accountable for this fact. Climatic and weather influences, therefore, are of great importance among the outside forces bearing on the patient's welfare and health.

Of particular interest are the observations of Paul and Freese<sup>27</sup> on the common cold in an Arctic community isolated in winter. They found that apparently an unfavorable environmental factor, such as a sudden drop in atmospheric temperature, was not necessary for the development of an epidemic of colds. The arrival of the first boat of the shipping season, however, was usually followed by an epidemic involving the whole community in a short while. This suggests, as they say, that the introduction of the virus from the outside is more important than the climate. Also, trappers who fell through the ice did not develop colds during the winter and spring but did so if this happened after the men had been to town in the summer and fall. Thus, sudden chilling of the body may bring on an attack in a person who has had a recent infection or a recent contact, but only if such a condition accompanied the chilling.

Outbreaks of colds were noted by Paul on the "Carnegie" when the ship entered a cold current from warmer waters even though it had been out of port for days or weeks. This suggests that exposure to cold may in some way activate the virus in a group after it has failed to produce infection for many days or weeks preceding the outbreaks. According to Paul, it seems plain that a more careful definition of the host and environmental factors which favor the invasion of the virus of the common cold is necessary before the spread of the infection can be effectively controlled.



### III THE UPPER RESPIRATORY INFECTIONS ABOARD A DESTROYER

No doubt the medical officers of other warships in our zone have observed the same factors as herein noted. If so, the significance of our observations will be greatly increased, for as it stands the personnel of one destroyer accounts for only a few hundred men among the thousands of individuals who are now living under similar conditions.

TABLE I

Incidence by Months of 607 Visits to Sick-Bay for Various Upper Respiratory Diseases

| Months    | Visits to Sick-Bay | Months      | Visits to Sick-Bay |
|-----------|--------------------|-------------|--------------------|
| December  | 126                | October     | 3                  |
| January   | 16                 | November    | 12                 |
| February  | 45                 | December    | 2                  |
| March     | 120                | January     | 40                 |
| April     | 20                 | February    | 8                  |
| May       | 56                 | March       | 1                  |
| June      | 4                  | April 1-15  | 3                  |
| July      | 5                  | April 15-30 | 12                 |
| August    | 28                 | May         | 12                 |
| September | 6                  | June        | 88                 |

Compare with figure 1

TABLE II

Incidence by Months of 61 Admissions to Sick List for Various Upper Respiratory Diseases

| Months    | Number of Admissions to Sick List | Months   | Number of Admissions to Sick List |
|-----------|-----------------------------------|----------|-----------------------------------|
| December  | 8                                 | October  | 0                                 |
| January   | 2                                 | November | 0                                 |
| February  | 4                                 | December | 0                                 |
| March     | 22                                | January  | 2                                 |
| April     | 3                                 | February | 0                                 |
| May       | 12                                | March    | 0                                 |
| June      | 2                                 | April    | 0                                 |
| July      | 0                                 | May      | 0                                 |
| August    | 1                                 | June     | 5                                 |
| September | 0                                 |          |                                   |

Compare with figure 2

TABLE III

Various Diagnoses in Cases of Upper Respiratory Infections Admitted to Sick List Over a Period of 19 Months

| Diagnosis              | Number of Cases |
|------------------------|-----------------|
| Bronchitis, acute      | 3               |
| Catarrhal fever, acute | 24              |
| Influenza              | 0               |
| Laryngitis, acute      | 1               |
| Pharyngitis, acute     | 16              |
| Septic sore throat     | 1               |
| Tonsillitis, acute     | 15              |
| Tracheitis, acute      | 1               |

The personnel of a ship at sea constitutes in effect a mobile, isolated community, a small community it is true, when we are speaking of a destroyer That iso'ation is maintained as long as the ship remains at sea or, at least, does not have contact with persons ashore, particularly persons

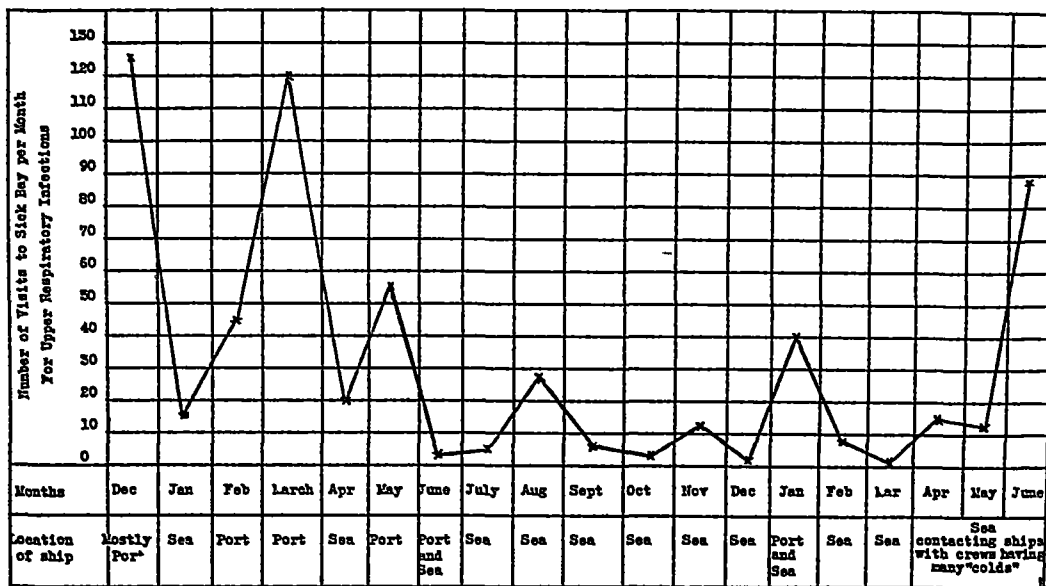


FIG 1

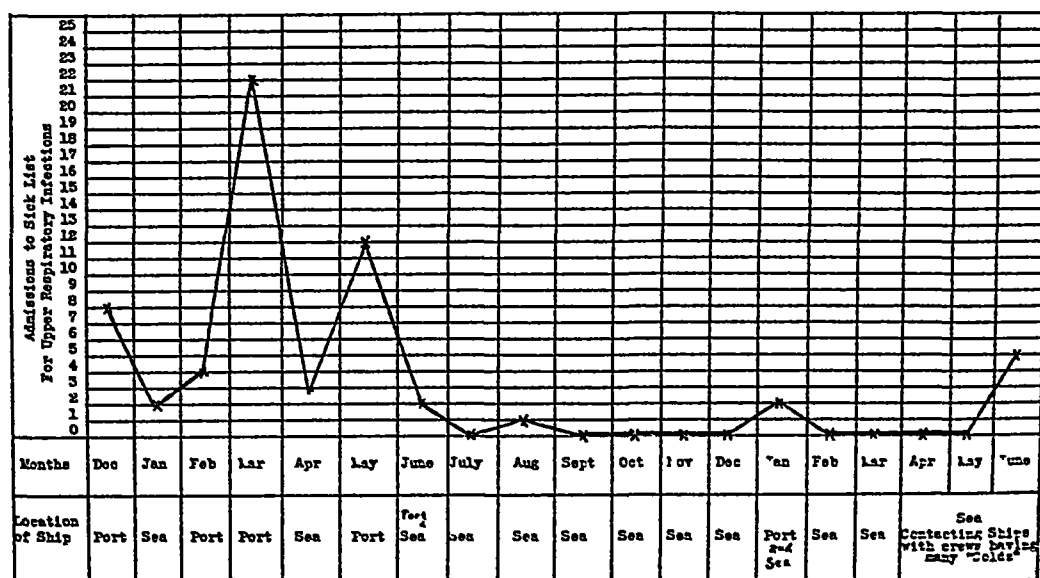


FIG 2

organized into communities Additional points in regard to individuals living aboard warships, particularly destroyers, are the closeness of their quarters and the crowding into small spaces By this it is implied that as far as respiratory tract infections are concerned among these individuals, it is

"all for one and one for all", i e, contact is sufficiently close that nearly all men are exposed to one another and what respiratory infection one has, will be spread to all aboard who are susceptible

With these points in mind, the following facts are presented

During a period of 19 months, there was a total of 607 visits to the sickbay of this ship for upper respiratory infections of varying degrees of severity. Of these 61 were severe enough to require admission to the sick list, i e, those whose illnesses were febrile and who required relief from duty for a period of more than 24 hours. These facts are indicated in tables 1, 2, and 3 and in figures 1 and 2

Although it is impossible to indicate specifically the data concerning the ship's movements during this time, the circumstances surrounding these marked variations in respiratory infections aboard may be presented

|           |                                 |           |          |                                |        |           |
|-----------|---------------------------------|-----------|----------|--------------------------------|--------|-----------|
| December  | Temperate zone                  | Mostly in | November | Tropics                        | At sea | Fatigue   |
|           | port                            |           |          |                                |        |           |
| January   | Tropics                         | At sea    | December | Tropics                        | At sea | Severe    |
|           |                                 |           |          | fatigue                        |        |           |
| February  | In the north                    | In port   | January  | Tropical and temperate areas   |        |           |
|           |                                 |           |          | At sea and in port             |        |           |
| March     | In the north                    | In port   |          |                                | Rest   |           |
| April     | Temperate zone                  | At sea    | February | Tropics                        | At sea | Fatigue   |
| May       | In the north                    | In port   | March    | Tropics                        | At sea | Mild      |
|           |                                 |           |          | fatigue                        |        |           |
| June      | Temperate and tropical zones    |           | April    | Tropics                        | At sea | Increased |
|           | Partially in port and partially |           |          | contact with other ships about |        |           |
|           | at sea                          |           |          | 15th                           |        |           |
| July      | Tropical zone                   | At sea    | May      | Tropics                        | At sea | Increased |
|           |                                 |           |          | contact with other ships       |        |           |
| August    | Tropics                         | At sea    | June     | Tropics                        | At sea | Contact   |
| September | Tropics                         | At sea    |          | with ship having many "colds"  |        |           |
| October.  | Tropics                         | At sea    |          | aboard                         |        |           |

Along with fatigue during the months of November, December, February and March were also conditions which made dietary factors irregular with possibly low vitamin intake, lack of milk and fresh vegetables. There was great loss of sleep on the part of all hands, and opportunities for bathing were at fairly wide intervals (two to three days). Also during much of this period, the personnel were frequently wet with profuse rains. The factor of body chilling, however, was usually absent. Beginning with the latter part of April there was increased contact with other ships. One of these ships (in June) had a large number of men aboard with "colds."

#### COMMENTS

By comparing these circumstances with the figures and graphs showing incidence of upper respiratory infections, it is readily seen that there is a close relationship between contacts with the shore and increased number

of respiratory infections. Thus, there are peaks in December, February-March, May and January. There is a slight elevation of incidence in August. This is not completely understood. There was considerable fatigue during this month, to which the personnel may not yet have become adapted. Otherwise, such factors as fatigue with its usually discussed "lowered bodily resistance," irregular dietary and bowel habits, impaired sanitation measures (bathing, etc.), wetting of body surface by rains, etc., all seemed to be without effect in bringing about an increased incidence of upper respiratory infections when adaptation to these factors had occurred. These observations are in accord with those of Paul and Freese<sup>27</sup> concerning Spitsbergen, and suggest that the introduction of the infectious agents by outside contacts is the important factor in initiating increased incidence of these diseases. Also, since incidence seems to fall off so abruptly (within two weeks or so), "carriers" among our own personnel were apparently of no significance, owing either to the short period of survival or of infectiousness of the causative agents which they might have carried, or to a possible, though rather far-fetched, conception of an inter-immunity of the personnel, each to whatever agents his fellows might carry. In regard to this latter, though several groups of healthy individuals were received aboard during the months of July through December, none of them seemed to fall victim to any of our possible agents, nor did their arrival bring about a definite outbreak among the personnel aboard. It is possible that the slight increases noted during April and May were due to this fact, for most of the new personnel arrived during these months. There is quite a definite rise in admissions to sick list and visits to the sick-bay in June. It is felt that these upper respiratory infections had their origin in contact with another ship whose personnel had numerous "colds."

#### SUMMARY AND CONCLUSIONS

Upper respiratory infections have been dealt with as a group, taking into account their statistical importance, differential diagnosis, pathology, complications, and epidemiological considerations. The facts concerning the incidence of these infections aboard a destroyer and the various conditions of climate, etc., surrounding them are presented. It has been noted that outside contacts (with persons ashore, in other ships, etc.) are apparently the most important factor in bringing about an outbreak of these infections. Without such contacts, within a period of two to three weeks (or less), upper respiratory infections tend to diminish progressively, approaching an extremely low level. This seems important, since if such can happen in a small "community" (the personnel of a destroyer), it can possibly be brought about ashore in larger communities.

In consideration of factors which may have allowed the relative disappearances and later produced reappearances of upper respiratory infections aboard, the following statements are made

(1) Outside contacts bring about increased incidence In the absence of outside contacts, respiratory infections tend to disappear within two to six weeks

(2) In general, no sudden, severe climatic changes were encountered Gradual changes of this nature apparently have little or no influence on the problem

(3) In the absence of contacts, such adverse factors as long continued fatigue (to the point of exhaustion), monotony, irregular and possibly slightly deficient (qualitatively) diet, loss of sleep, inaccessibility of bathing facilities, seem to be of no importance

(4) These observations serve to confirm the significance of "contacts" for this group of infections Furthermore, the "set-up" (viz mobility and interval environmental changes) afforded the analogue of serial experimental observations Through this available means the importance of "contact" is emphasized, while that of such factors as fatigue, loss of sleep, exposure and the like is minimized Thus, stated simply, though most difficult to put into practice, the control of this important group of diseases seems to lie in the control of "contacts"

#### BIBLIOGRAPHY

- 1 KLEFER, C S Common respiratory infections, Jr Am Med Assoc, 1943, cxxi, 802-806
- 2 MASSEY, A, and PEARSON, R C M Sick absence among munitions workers, Brit Med Jr, 1942, ii, 694
- 3 SMILEY, D F The incidence of acute respiratory infections, the experience of the U S Navy since 1781, U S Nav Med Bull, 1944, xl, 17-26
- 4 LUDWICK, J E, and JONES, B C, JR Observations on "catarrhal fever," U S Nav Med Bull, 1943, xli, 573
- 5 The personnel of Nav Lab Research Unit No 1, U of California The diagnosis of influenza and catarrhal fever, acute, a plea for accurate diagnosis, U S Nav Med Bull, 1944, xlii, 27-33
- 6 WARREN, SHIELDS The pathological aspects of acute pharyngeal infections, U S Nav Med Bull, 1943, xli, 1252-1258
- 7 RUSK, H A, and VAN RAVENSWAAY, A C Sulfadiazine in respiratory tract infections its value in treatment during winter of 1942-1943 at Jefferson Barracks, Missouri, Jr Am Med Assoc, 1943, cxxii, 495
- 8 DOLOWITZ, D A, LOCK, W E, HAINES, H L, WARD, A T, and PICKRELL, K L The prevention of ear and nasal sinus complications of the common cold, Jr Am Med Assoc, 1943, cxxiii, 534-536
- 9 TURNBULL, F M, HAMILTON, W F, and GEORGE, M J, JR Sinusitis and infections secondary to the common cold Treatment with stabilized aqueous solution of sulfathiazole sodium with desoxyephedrine hydrochloride, Jr Am Med Assoc, 1943, cxxiii, 535-538
- 10 SILVERTHORPE, M, and PATTERSON, M Further studies with *Hemophilus influenzae*, Type B, Part II, A survey for the presence of *H influenzae*, type B, Canad Pub Health Jr, 1943, xxxiv, 178
- 11 BURNET, F M, BLUFRIEDGE, W I B, BULL, D R, and CLARK, E Investigations of an influenza epidemic in military camps in Victoria, May 1942, Med Jr Australia, 1942, xxi, 371
- 12 EATON, M D, and MARTIN, W P An analysis of serological reactions after vaccination and infection with the virus of influenza A, Am Jr Hyg, 1942, xxxvi, 25

- 13 Personnel of Naval Laboratory Research Unit No 1, U S N R of California, Distribution of influenzal antibodies among vaccinated and unvaccinated naval personnel, U S Nav Med Bull, 1943, xli, 426-431
- 14 FRANCIS, T J, PEARSON, H E, SULLIVAN, E R, and BROWN, P M The effect of subcutaneous vaccination with influenza virus upon the virus-inactivating capacity of nasal secretions, Am Jr Hyg, 1943, xxxvii, 294
- 15 BULL, D R, and BURNET, F M Experimental immunization of volunteers against influenza virus B, Med Jr Australia, 1943, xxx, 389
- 16 BURNET, F M Immunization against epidemic influenza with living attenuated virus, Med Jr Australia, 1943, i, 385
- 17 MAWSON, J, and SIVAN, C Intranasal vaccination of humans with living attenuated virus strains, Med Jr Australia, 1943, xxx, 394
- 18 BODILY, H L, and EATON, M D Specificity of the antibody response of human beings to strains of influenza virus, Jr Immunol, 1942, xlv, 193
- 19 HENLE, W, HENLE, G, and STOKES, J, JR Demonstration of the efficacy of vaccination against type A by experimental infection of human beings, Jr Immunol, 1943, xlv, 163
- 20 Editorial Influenza receptolysin, Jr Am Med Assoc, 1943, cxxxiii, 288
- 21 HIRST, G K Adsorption of influenza virus on cells of the respiratory tract, Jr Exper Med, 1943, lxxviii, 99
- 22 SIEGEL, M, RANDALL, M G, HECKER, M D, and REID, M A study on the value of mixed "oral cold vaccine," Am Jr Med Sci, 1943, ccv, 687
- 23 COWAN, D W, DIEHL, H S, and BAKER, A B Vitamins for the prevention of colds, Jr Am Med Assoc, 1942, cxx, 1268
- 24 FELDERMAN, L Influenza—the number two concern of the medical profession, Med Rec, 1942, clvi, 229
- 25 MILLS, C A American Health Reports climate and disease, Jr Am Med Assoc, 1943, cxxxiii, 551-557
- 26 LOCKE, A Lack of fitness as the predisposing factor in infections of the type encountered in pneumonia and in the common cold, Jr Infect Dis, 1937, lx, 106
- 27 PAUL, J H, and FREESE, H L An epidemiological and bacteriological study of the "common cold" in an isolated Arctic community (Spitsbergen), Am Jr Hyg, 1933, xvi, 517

# THE FUNCTIONAL CONSEQUENCES OF CORONARY OCCLUSION \*

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THE symptomatology of acute coronary occlusion is too well-known to require detailed redescription. Let it suffice for our purpose to recall three outstanding phenomena, so serious for the patient and so informative for the physician in formulating a diagnosis. 1, the agonizing pain, crescendo in character and radiating from a focal region over the sternum outward to the left arm, upward to the throat, and downward to the epigastrium, 2, the irregular or rapid action of the heart, and 3, the signs of cardiovascular failure, such as hypotension, feeble pulse, venous congestion, cutaneous pallor, sweating, cyanosis, etc., which frequently raise the questions as to whether circulatory failure is of central or peripheral origin and whether the diagnosis of circulatory collapse or shock is warranted. It is with functional conditions leading to these signs and symptoms *during an attack* rather than with those which prove immediately fatal or those which persist after recovery that my discussion is chiefly concerned. Pathological studies have not shed much light upon this stage of coronary occlusion except through speculative inferences, whereas experimental studies—mostly on dogs—have revealed the nature of the functional disturbances and furnished us with the guiding principles in interpreting the clinical symptomatology, in formulating a prognosis and, in some instances, in directing our therapeutic trends. I venture to analyze some of these early functional changes, because it has been my privilege to carry out many experiments pertaining to these problems myself, to direct others in my laboratory and to witness still others of colleagues in our school—an experience that gives one first-hand impressions not to be gained from investigations of others, about which one can only hear or read.

## FUNCTIONAL ACTIVITIES OF THE NORMAL MYOCARDIUM

Ventricular muscle has the fundamental attribute of *excitability* by virtue of which minute electrical potentials traveling over muscle systems by a process called conduction, cause every fraction to contract or shorten against the resistance of intraventricular and aortic pressures. In order to contract, each muscle fraction must have an impulse conducted to it and must contain the chemical energy-material (probably adenylypyrophosphate) which on explosion is converted into contractile stress. It is generally believed that this explosion occurs under anaerobic conditions, but that new material is continually reformed during diastole through oxidative processes. In short, we

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may say that release of a "metabolic spring" leads to contraction and the rewinding of the spring takes place during diastole. The chief importance of an adequate flow of blood through the myocardium, therefore, consists in supplying the oxygen for rewinding the machinery and in carrying away the products of combustion. That anoxia, interference with oxidation, and accumulation of waste products with decrease in pH exert deleterious effects on the intact heart, was beautifully demonstrated by Tennant in my laboratory. Tennant<sup>1</sup> exposed and cannulated a branch of the *ramus descendens*

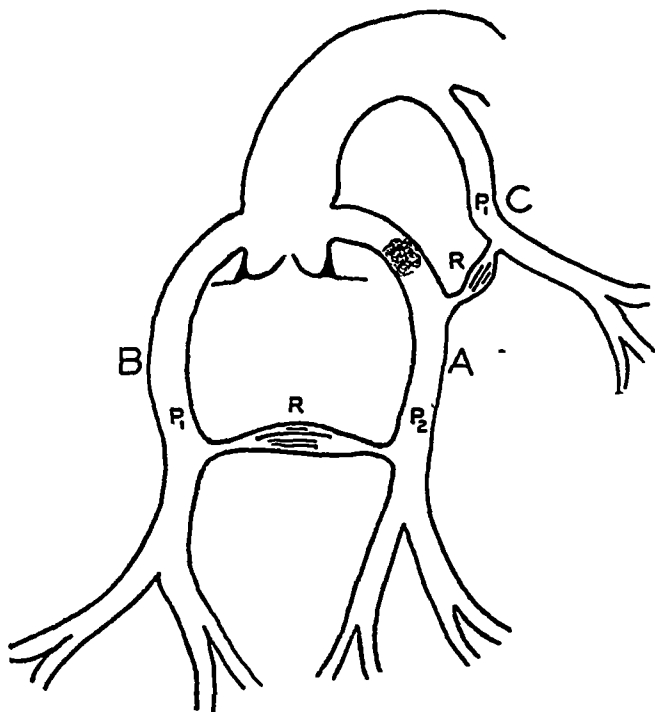


FIG 1 Scheme showing potential coronary and extracoronary communications that may develop into serviceable channels after occlusion of a major ramus but which are functionally unimportant in normal hearts. Discussion in text.

and connected it to a reservoir of heparinized blood under 100 mm Hg pressure. By clamping the main branch and allowing such blood to flow through the myocardium, normal contractions continued unabated. But when he added to this blood such agents as KCl (which blocks conduction of impulses), sodium cyanide (which destroys oxidative enzymes) or lactic acid, the region supplied failed to contract. Similar effects occur when the regions are perfused with solutions of reduced hemoglobin or with fully oxygenated Locke's solution which is unable to carry adequate volumes of oxygen for the working heart in the body.

#### THE EFFECTS OF CORONARY OCCLUSION

In a normal heart, occlusion of any major coronary ramus or its main branches results in an almost immediate failure in oxygen supply, because such anatomical anastomoses as exist are not in fact functional. They are



normally of such small diameters that a sufficient pressure-differential does not exist to irrigate the territory supplied by the main coronary branch. The elementary hemodynamics are elucidated in figure 1. Suppose two adjacent vessels, A and B, supply separate territories of myocardium and that communications (R) exist. Since both of these vessels come from the aorta and since pressures  $P_1$  and  $P_2$  within them are equal, no transfer of blood occurs through the communications regardless of their size. If vessel A be occluded, the volume flow transferred from B to A depends on the pressure difference  $P_1 - P_2$ , on the square of the cross-sectional area of anastomosing vessels and inversely on the length of the vessels and the viscosity of the blood. Since the last three factors determine impedance to flow they are generally designated as vascular resistance (R). Thus, volume flow  $= P_1 - P_2 / R$ . Obviously the same conditions apply to possible extracoronary

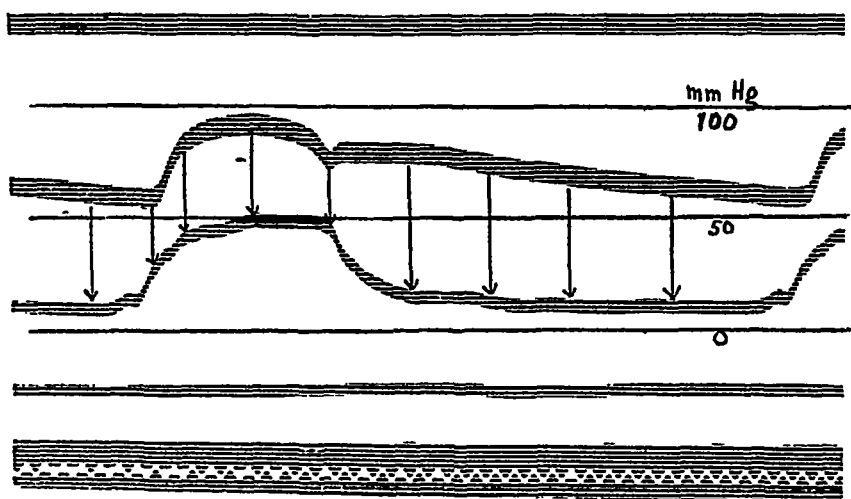


FIG 2 Optical pressure curves showing range of pressures in an unoccluded (upper) and occluded coronary ramus (lower). Arrows indicate pressure differences at various moments of the cardiac cycle. These are not sufficient to force blood through normal collaterals.

communications represented diagrammatically by vessel C in figure 1. Now, studies of collaterals between coronary vessels (A, B) and between coronary and extracoronary vessels (A, C) by injection methods have shown that the communications are normally sparsely distributed and of small size. When one coronary ramus is clamped and the blood flow from its peripheral end is measured, it generally amounts to only a few drops per minute. Measurements of pressure in an open and an occluded vessel have revealed that the pressure does not approach zero in the latter but rises significantly during systole, owing to compression of intramyocardial branches, thus decreasing the pressure differential materially. Such curves illustrating the effective pressure differences which exist between patent and occluded vessels during the cardiac cycle are shown in figure 2. On the basis of observations such as these, the prediction could be made that the coronary vessels are functional end-arteries. That such collaterals are really inadequate was demonstrated

more crucially in experiments by Tennant and myself<sup>2</sup> by recording contractions from an area supplied by a coronary ramus (e.g., *ramus descendens anterior*) before and after the main coronary was clamped. We found, as illustrated in figure 3, that approximately within 60 seconds the area studied no longer shortened during the period of systolic ejection, but brusquely expanded during isometric contraction under the force of rising ventricular pressure. The stretching of such ischemic areas can also be demonstrated by aid of moving pictures and has in fact been recorded after coronary occlusion in man by the aid of fluoroscopic and roentgenkymographic methods<sup>3, 4, 5</sup>. Indeed, such procedure has been suggested as an additional means for localizing the ischemic area in man and in estimating its extent. Subsequently, H. Green and I,<sup>6</sup> using similar methods, were unable to restore functional contractions in the ischemic area of dog's hearts by use of xanthis, nitrites,

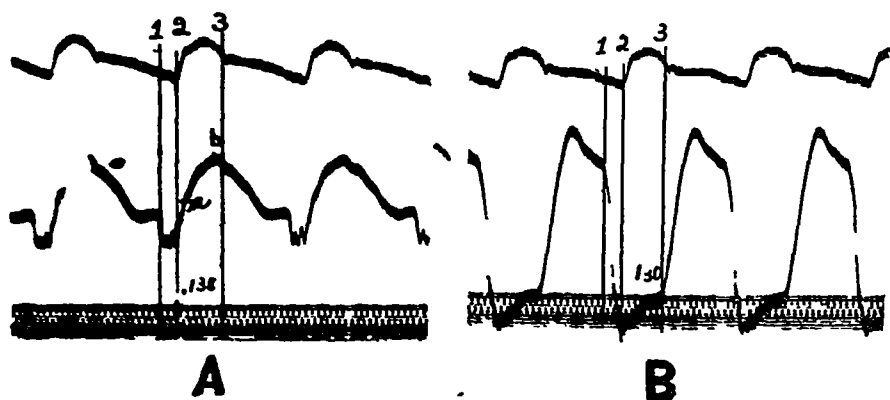


FIG 3 Aortic pressure curves (upper curve) and myographic records from a region supplied by the ramus descendens anterior (lower curve). A, normal—note that the area shortens during systolic ejection as indicated by upward stroke during interval 2-3. B, 60 seconds after occlusion of the ramus descendens anterior—note that the area expands brusquely during isometric contraction as shown by pronounced downstroke during interval 1-2 and contracts very little during systolic ejection (2-3).

adenylic compounds or epinephrine, indicating that serviceable communications cannot be established in normal hearts by drugs reputed to dilate coronary vessels.

Although collateral circuits are certainly of no importance in furnishing oxygenated blood to a potentially infarcted area in hearts of normal dogs—and quite likely in normal hearts of man—it has also been experimentally demonstrated that they can become serviceable when the main vessel is gradually occluded. The mere demonstration that progressive reduction in the lumen of a main vessel by operative procedures increases the number and size of communications by which one set of arteries can be forcibly injected from another in dead hearts is suggestive, but does not demonstrate that such blood flows through capillaries in the myocardium. The same is true of observations that the pressures and flow in the peripheral end of an occluded vessel augments (Mautz and Gregg<sup>7</sup>). However, the demonstrations by Tennant and Bright in our laboratory that sudden complete occlusion of

the ramus in such hearts is not followed by abolition of contraction in the areas which it supplies is crucial evidence for the adequacy of such newly formed collaterals. It should be added, however, that it has not been demonstrated that development of such efficient collaterals is limited to inter-coronary communications, it is highly probable indeed that extracoronary communications (illustrated in figure 1) also develop at the base of the heart. Such development of coronary collaterals through slow narrowing of a main vessel probably explains the occasional necropsy reports of cases in which one ramus had been completely occluded for years without creation of infarcts in the territory which it supplied. Finally, it should be mentioned that it has been demonstrated morphologically that the arterioles, capillaries, sinusoids and venules of the myocardium connect with the ventricular cavities.<sup>8</sup> However, the bulk of experimental evidence strongly suggests that they are not functionally important as collateral supplies when a main coronary is occluded.

The practical conclusion from such experimental observations would seem to be that antecedent gradual narrowing of a main coronary vessel favors the development of collaterals which may be adequate to supply a neighboring territory when sudden complete occlusion of its main branch supervenes.

#### DYNAMIC CONSEQUENCES OF ABOLITION OF CONTRACTION IN ISCHEMIC AREAS

Although a search of the literature reveals that experimenters previous to Tennant and myself had noticed—or believed they had observed—an absence of contraction or bulging of an ischemic region, it is certain that its significance for the dynamics of the heart beat and circulation were not appreciated by them. However, Orias<sup>9</sup> reporting from my laboratory in 1932 had actually predicted that changes in the form, amplitude and duration of ventricular pressure curves and the consequent changes in the dynamics of the whole circulation must be initiated by just such absence of contraction in an ischemic area. His analysis and all subsequent studies lead clearly to the conclusion that the cardiac and circulatory embarrassment which follows coronary occlusion in man is also initiated by such deletion of contracting muscle blocks. This not only reduces the total myocardial force available for raising intraventricular tension but some of this pressure is spent in stretching the ischemic area and is thus lost for expelling blood into the aorta. The immediate consequences are shown in records A and B of figure 4. The ventricular pressure maximum is lowered, systolic discharge is reduced, pulse pressure in the aorta is decreased, and systolic and diastolic pressures fall. In addition, the period during which blood is expelled is reduced from 134 to 121 second, as a result of the deletion of contracting myocardial fractions. However, as shown in curve C of the same figure, taken four minutes later, the heart has compensatory mechanisms by means of which dynamic conditions can be restored to normal, provided the remain-

ing myocardium is in good responsive condition I may add parenthetically that while this accords with general clinical belief, the experiments just quoted are to my knowledge the only ones on record which demonstrate that compensation occurs not through improvement of circulation in the affected area but through enhanced action of the myocardium which is not involved. Experiments such as these do still more, they suggest the mechanism by virtue of which the rest of the muscle responds promptly to the needs

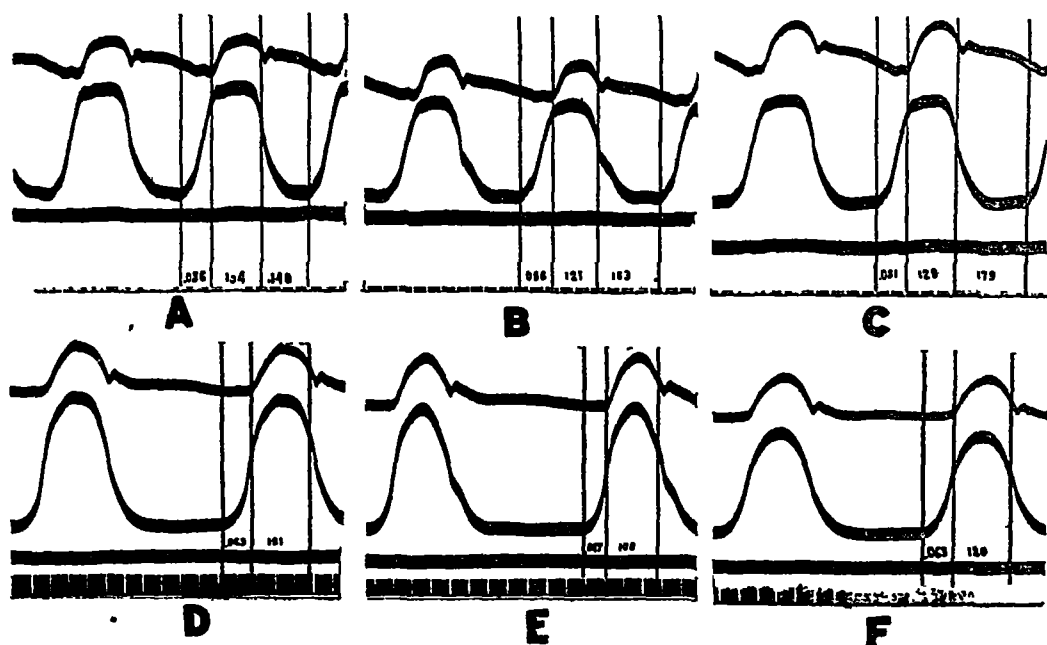


FIG 4 Aortic pressures (upper curves) and left ventricular pressures (lower curves) A, control B, shortly after occlusion of ramus descendens anterior C, after development of compensation D, control from another animal E, shortly after occlusion F, later, with failure of compensation Discussion in text.

For details, other sources must be consulted<sup>10</sup>. Briefly, the following series of events is involved. During hypodynamic beats (curve B) the ventricles expel less blood, the accumulating systolic remainders added to oncoming blood raise diastolic pressure in the ventricles and stretch the viable muscle, this muscle, in accordance with the law of initial tension and length—sometimes called Starling's law—contracts more vigorously, thereby restoring cardiac output and arterial pressures to normal. However, not all dogs under anesthesia and submitted to operative procedures necessary for exposing the heart react as well, because the viable portion of the myocardium may not respond to stretch. In that event, as shown by curves D, E, F of figure 4, obtained from another dog, ventricular pressures reach the lower maxima, the pulse pressure decreases and arterial pressure falls progressively. The ventricles, atria, pulmonary vessels and veins fill with blood, in short "back-pressure effects" become operative.

## CIRCULATORY FAILURE, SHOCK AND COLLAPSE

Although it is clear from experimental studies that myocardial failure is the crux of the circulatory failure which follows, secondary reactions take place which change the picture both in dogs and in man in such a way that dynamically and symptomatically it is often difficult to separate from that of experimental or clinical shock due to loss of blood or plasma. When this occurs the clinician is apt to declare that a state of circulatory failure, shock or collapse exists. Is such terminology warranted? The answer depends on whether we choose to make the diagnosis of "shock" on the basis of clinical signs and symptoms or on the basis of which part of the cardiovascular system is primarily affected and ultimately defaults. The similarity of clinical syndromes following coronary occlusion and loss of blood or plasma is due to the fact that, in both cases, cardiac output is decreased, but for different reasons. The same compensatory mechanisms are, therefore, set in operation regardless of whether reduced systolic discharge is primarily due to defective return of blood, as in hemorrhage, to hindrance of ventricular filling, as in pericardial effusions, or to depression of the total contractile capacity of the ventricles, as in uncompensated cases of acute coronary occlusion. One of the consequences of lowering arterial pressures is that moderator vascular reflexes operate to cause generalized vasoconstriction,—in the viscera as well as in the muscles and skin. Now it seems probable as a result of recent studies that visceral constriction acts dominantly to increase total peripheral resistance, thus helping to sustain arterial pressure, but that constriction of skin vessels acts chiefly by diverting blood from the capacious skin reservoir to internal organs. In circulatory failure due to loss of blood or plasma this transfer of blood acts in a compensatory manner by increasing the volume of blood returned to the heart with the result that cardiac output and arterial pressures are raised. In coronary occlusion it merely tends to intensify the engorgement and adds to the volume of blood that the defective myocardium cannot move. Moreover, cutaneous constriction is intensified by reflexes associated with the intense pain and so helps to create a surface appearance which cannot be distinguished from that of shock due to peripheral circulatory failure. In addition, the pulmonary congestion induces respiratory reflexes which lead to hyperpnea or dyspnea of a grade rarely seen in shock. Since venous flow is retarded, cyanosis is generally more intense than in shock due to loss of blood or plasma, but this difference may not be conspicuous.

It is obvious that if clinicians insist in making the diagnosis of shock on the basis of low blood pressure, small pulse, feeble rapid heart action, clammy, cold, pale or cyanotic skin, drawn expressions, etc., without regard to the initiating mechanism and mode of terminus, the circulatory failure following coronary occlusion comes in the category of clinical shock. Scientifically, however, the circulatory failure of coronary occlusion does not belong to the category of shock, for unlike conditions to which this term is re-

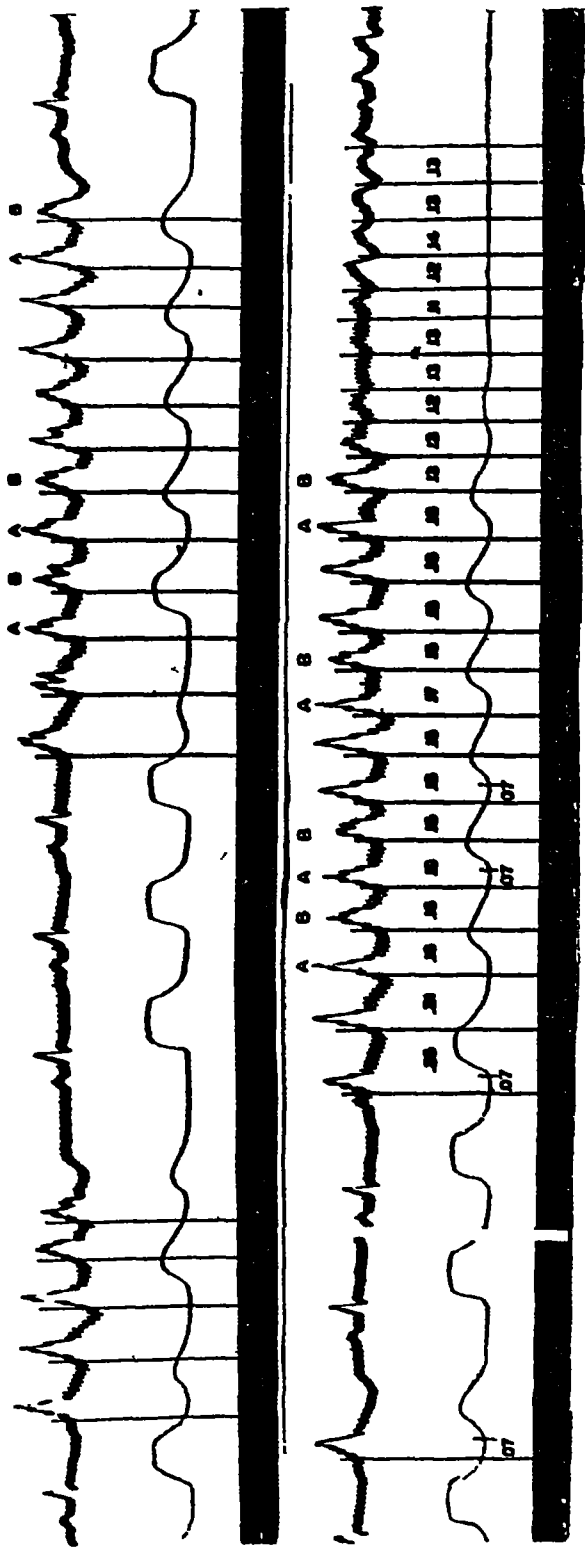


FIG 5 Electrocardiograms, Lead II (upper records) and left ventricular pressure curves (lower records) from two animals showing development of short tachysystolic periods and the development of ventricular fibrillation in the lower set of records Discussion in text

stricted by common consent it is not initiated by reduction in effective circulating volume and venous return and death does not ordinarily occur as a result of an irreversible state in the peripheral vessels. For therapeutic reasons, if for no other, the conditions should be differentiated in our terminologies, in one, transfusions improve the circulation, in the other they would only embarrass the heart.

### CARDIAC IRREGULARITIES

As soon as an area of myocardium becomes ischemic, spontaneous foci tend to develop from which impulses are discharged. These give rise to premature contractions or transient periods of ventricular tachycardia. When the impulses are not emitted in regular sequence but in an accelerating manner, fatal ventricular fibrillation eventuates. Although the development of such arrhythmias has long been known to clinicians and experimentalists alike, the conditions which favor or induce them remain obscure. My associates and I have, for several years, studied the physiological condition of the ischemic muscle from various angles, and while many interesting facts regarding its state of excitability, conductivity, polarization and feeble efforts at contractions have been established, the fundamental explanation for the development of rhythmic or sporadic foci is still undecided.<sup>11, 12</sup>

The occurrence of cardiac irregularities or tachycardia is detrimental for maintaining a balance of the circulation even under normal conditions of the circulation. However, owing to the operation of various compensatory mechanisms, they rarely prove significant. When, however, after coronary occlusion, these compensatory mechanisms are already utilized and particularly when the maintenance of a good circulatory balance is being barely accomplished, the supervention of irregularities may cause serious cardiac decompensation. They intensify "back pressure effects," reduce cardiac output, and lower arterial pressure. Furthermore, not every ectopic excitation which develops and is recorded in electrocardiograms elicits a mechanical systole. This is illustrated in the two records of figure 5. In the upper set of records, the standard Lead II reveals two groups of excitations constituting short tachysystolic paroxysms. The ventricular pressure curve shows only half the number of mechanical systoles, generally of reduced size. Obviously alternate excitation waves (B) released in the ischemic area are ineffective, because they arrive during the refractory periods of the functioning muscle. The lower set of records shows a somewhat longer series of similar excitations which are alternately effective (A) and ineffective (B) and, as the frequency increases the ventricles fibrillate. The danger always exists that such accelerating rhythms leading to fibrillation may develop at any time. The onset of such fibrillation is the only reasonable explanation for sudden death, either at the onset or during the course of coronary occlusion.

Ventricular fibrillation is an "incoordinate" type of contraction which produces no effective beats. As a result, arterial pressure falls abruptly to very low levels and death from cerebral anemia supervenes. For a number of years, various members of my staff and I have been interested in studying the mechanisms of fibrillation and its mode of onset. The bulk of experimental evidence indicates that fibrillation once developed represents a condition in which an incoordinated reentry of impulses occurs because blocks occur in various regions and impulses are forced to zigzag their way through cardiac tissue. While some of them return ultimately to some part of the original path, the locus of reentry is not definite, as Lewis believed to be the case in atrial fibrillation. As to the mode of onset, we are convinced that the stage of fibrillation is immediately preceded by a series of tachysystolic discharges from some single focus. When, as shown in figure 5 (lower set records), their frequency increases beyond a critical level, blocks develop which prevent an orderly excitation of viable myocardium. Consequently some impulses reenter and the ventricles fibrillate.

The question still remains as to the cause of these repetitive focal discharges and the conditions which give rise to them. As regards the latter, we have explained and obtained evidence for each of two possibilities. Wegria, Pinera and Wiggers<sup>11</sup> obtained evidence that the fibrillation threshold in the ischemic area is decreased to such an extent that a chance premature natural impulse arising during the late moments of systole may give rise to a repetitive series of discharges. Harris and Guevara Rojas<sup>12</sup> favor the view that electrotonic currents develop across the margins of an ischemic area which, as in nerve cells and fibers, develop a rapid repetitive accelerating rhythm.

### CARDIAC PAIN

Cardiac pain and its concomitants are probably the most outstanding features of coronary occlusion, although many cases have been reported in which significant pain appears to have been absent. Experimental studies have demonstrated that the impulses giving rise to sensations of pain travel over the sympathetic system. Their pathways are probably as follows: (a) *via* left middle cardiac nerves to the middle cervical ganglion, through the cervical cord and stellate ganglion, entering the cord by white rami of the first to the fourth or fifth thoracic ganglia, (b) *via* left inferior cardiac nerves to the stellate ganglion, and thence as above, (c) *via* numerous direct connections between the heart and left upper five or six thoracic nerve roots.

The intense agonizing pain is made more unbearable by the development of disagreeable reflex actions. Segmental visceromotor reflexes increase the tonus of thoracic muscles which is appreciated in consciousness as an unpleasant sense of thoracic constriction. Reflexes to the stomach and gut cause reduction in tonus, and the drag thereby created causes a sinking feeling in the epigastrium. Nausea and vomiting often occur. The reflexes which, as in renal and biliary colic, cause pallor and coldness of the skin have



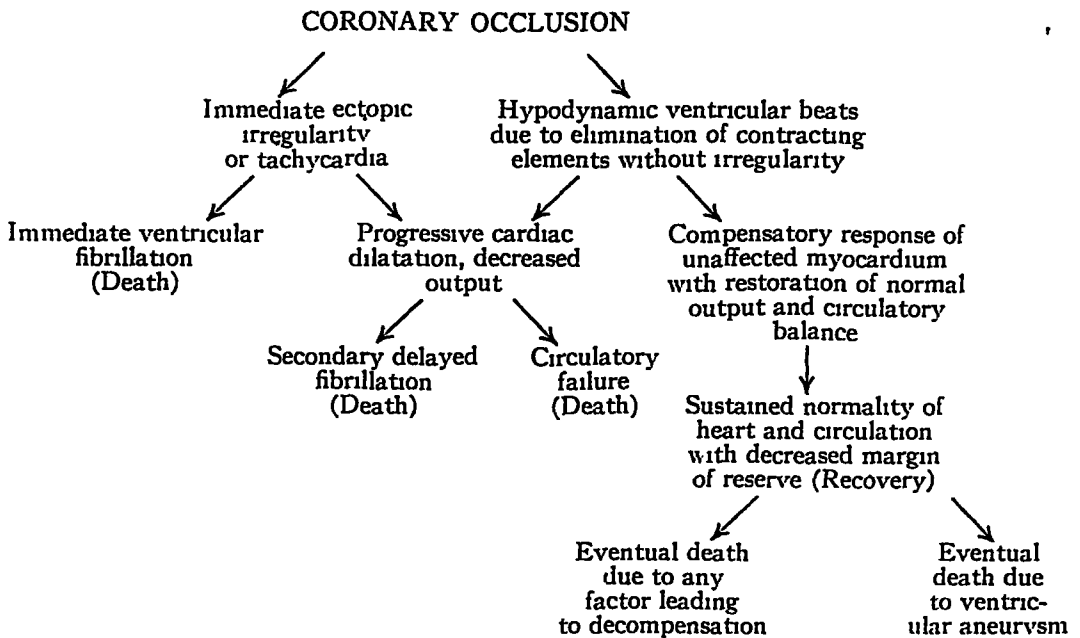
been mentioned. These and other concomitants of pain create a sense of impending dissolution and in some instances may even eclipse the pain itself.

mechanisms by which pain endings are stimulated in the heart have been investigated repeatedly. The bulk of experimental and clinical observation favors an origin within the ischemic area, but whether terminals are distributed throughout the muscle or are limited to connective tissue around blood vessels remains undecided. The preponderance of evidence indicates that chemical agents formed as a result of anaerobic metabolism act as stimuli, but their identity has not been discovered. To call them "toxins," as Lewis has done, does not advance our knowledge. Uncertainty also exists as to whether chemical substances accumulate to high local values because oxygen is lacking, or merely because they cannot be washed away. Finally, the possibility exists that mechanical stimulation may be a part. It has been suggested that this could occur as a result of (1) extreme distention of arteries proximal to a thrombus by high aortic pressure, (2) compression of sensory endings by contraction of vascular smooth muscle distal to occlusion, or (3) periodic stretching of the ischemic area. It has been found that similar periodic stretching of a skeletal muscle such as the nemus, evokes reactions which are unquestionably associated with pain. The fact that the pains are not rhythmic with the heart beat does not rule out such a possible origin for, in the conduction of impulses enunciated by peripheral summations of impulses occur which prevent the brain from recognizing their rhythmic character. Such an hypothesis would more readily account for the amelioration of pain by reduction of arterial blood pressure, for it could not affect the chemical agents within an ischemic region, and would cause less stretching of the walls in the affected area.

### SUMMARY

The myocardial effects of coronary occlusion are the immediate result of ischemia which may be defined physiologically as anoxia plus accumulation of products of anaerobic metabolism. This induces two dangerous conditions. It creates a functional state at or near the borders of the ischemic zones which favors production of ectopic beats which may lead to ventricular fibrillation and it eliminates contractile functions of the affected muscle, throwing the burden of work in maintaining an adequate cardiac output on the remaining muscle. If this muscle is able to respond in accordance with physiological rules, compensation occurs. If it does not or cannot maintain compensation, acute or progressive cardiac failure results which may lead to clinical symptoms and signs distinguished with difficulty from "shock" or circulatory failure of peripheral origin, but which are not such failures. The anoxia or chemical products of metabolism or possibly the mechanical stretching of the ischemic area excite pain and usually cause the suffering associated with coronary occlusion.

The sequential changes which early or late may lead to a fatal outcome are schematized in the following chart <sup>13</sup>



#### BIBLIOGRAPHY

- 1 TENNANT, R Factors concerned in the arrest of contraction in an ischemic myocardial area, *Am Jr Physiol*, 1935, cxiii, 677
- 2 TENNANT, R, and WIGGERS, C J The effect of coronary occlusion on myocardial contractions, *Am Jr Physiol*, 1935, cxii, 351
- 3 GUBNER, R, and CRAWFORD, J H Roentgenkymographic studies of myocardial infarction, *Am Heart Jr*, 1938, xviii, 8
- 4 SUSSMAN, M, DACK, S, and MASTER, A M The roentgenkymogram in myocardial infarction, *Am Heart Jr*, 1940, xviv, 453
- 5 MASTER, A M, GUBNER, R, DACK, S, and JAFFE, H L The diagnosis of coronary occlusion and myocardial infarction by fluoroscopic examination, *Am Heart Jr*, 1940, xx, 475
- 6 WIGGERS, C J, and GREEN, H D The ineffectiveness of drugs upon collateral flow after experimental coronary occlusion in dogs, *Am Heart Jr*, 1936, xi, 527
- 7 MAUTZ, F R, and GREGG, D R Dynamics of collateral circulation following chronic occlusion of coronary arteries, *Proc Soc Exper Biol and Med*, 1937, xxxvi, 797
- 8 For recent review see WEARN, J T Morphological and functional alterations of the coronary circulation, *Harvey Lectures*, 1940, xxxi, 243
- 9 ORIAS, O The dynamic changes in the ventricles following ligation of the ramus descendens anterior, *Am Jr Physiol*, 1932, c, 629
- 10 For details see WIGGERS, C J *Physiology in health and disease*, 4th ed, 1944, Lea and Febiger, Philadelphia, p 671
- 11 WIGGERS, C J, WEGRIA, R, and PINERA, B The effects of myocardial ischemia on the fibrillation threshold The mechanism of spontaneous fibrillation following coronary occlusion, *Am Jr Physiol*, 1940, cxvi, 309
- 12 HARRIS, A S, and GUEVARA ROJAS, A The initiation of ventricular fibrillation due to coronary occlusion, *Exper Med and Surg*, 1943, i, 105
- 13 After WIGGERS, C J *Physiology in health and disease*, 4th ed, 1944, Lea and Febiger, Philadelphia, p 726

# LYMPHOCYTOSIS IN THE CEREBROSPINAL FLUID <sup>1</sup>

By IRVING L. APPLEBAUM, Lt Col, M C, F A C P, JOEL SHRAGER, Major, M C, and WILLIAM PAFF, Major, M C

THE increase of cells in the cerebrospinal fluid may be either in the number of mononuclear lymphocytes or polymorphonuclear leukocytes and is invariably an indication of a pathological process. The predominant finding of polymorphonuclear elements points to a suppurative lesion and the scope of differential diagnosis is relatively limited. However, lymphocytosis presents a wider range of diagnosis, treatment and prognosis.

During an 18 month period (1942-1943) there were 72 cases of lymphocytosis in the cerebrospinal fluid caused by a variety of etiological agents

TABLE I  
Causes of Lymphocytosis in Cerebrospinal Fluid  
(72 Cases)

| Diagnosis   | No. Cases | Per (%) |
|---|-----------|---------|
| 1 Mumps meningo-encephalitis                                | 30        | 41.6    |
| 2 Acute lymphocytic meningitis, benign (cause undetermined) | 17        | 23.6    |
| 3 Syphilis of central nervous system                        | 7         | 9.7     |
| 4 Tuberculous meningitis                                    | 4         | 5.6     |
| 5 Chemical meningitis (intrathecal serum, etc.)             | 3         | 4.2     |
| 6 Acute encephalitis, cause undetermined                    | 2         | 2.8     |
| 7 Tetanus   | 2         | 2.8     |
| 8 Trauma of brain   | 1         | 1.4     |
| 9 Abscess of brain  | 1         | 1.4     |
| 10 Cysticercosis of C N S                                   | 1         | 1.4     |
| 11 Rabies   | 1         | 1.4     |
| 12 Lymphocytic meningitis associated with malaria           | 1         | 1.4     |
| 13 Guillan-Barre syndrome                                   | 1         | 1.4     |
| 14 Infectious mononucleosis                                 | 1         | 1.4     |

Table 1 is a résumé of the number and types of factors. The two most commonly encountered diseases were mumps meningo-encephalitis (41.6 per cent) and acute benign lymphocytic meningitis, cause undetermined (23.6 per cent).

*Clinical Aspects of Mumps Meningo-Encephalitis* Of 945 cases of epidemic mumps there were 30 (3.2 per cent) complicated by meningo-encephalitis with a lymphocytic reaction in the spinal fluid. Nine (30 per cent) of these 30 cases exhibited evidence of orchitis and three (10 per cent) suffered from pancreatitis, suggesting the widespread systemic invasion by the virus of mumps with a predilection for certain systems.

The onset was usually acute and occurred about 4.5 (average) days after the first signs of parotitis. On two occasions meningitic signs appeared a

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few days prior to evidence of salivary gland involvement and in one case central nervous system signs were elicited 12 days after the onset of parotitis. The more severe cases seemed to occur early in the course of mumps. Frontal headache was the most common complaint and then there followed in order of frequency increase in feverishness, vomiting, nausea, dizziness and nervous irritability. One patient had mild convulsions, which subsided after 24 hours.

An exacerbation of temperature occurred in all cases and averaged 3.5 days in duration. Except for nuchal rigidity, which was detected in 20 cases (66.6 per cent), there was a paucity of the classical signs of meningitis. Hyperactive reflexes were recorded in five cases, Kernig's sign was elicited in two cases, abnormal pupillary reflexes in two and Brudzinski's sign in one. These objective findings were transient and disappeared within 48 to 72 hours. There were no complications or deaths.

The average cell count of the spinal fluid was 298 per cubic millimeter (80 to 100 per cent lymphocytes) during the peak of the illness. The highest count was 1,298 cells and the lowest was 39 cells. Moderately increased pressure of the spinal fluid was noted in the majority of cases. Other studies of the spinal fluid, including the Wassermann reaction, the colloidal gold curve, glucose content and bacteriological culture, were normal. Several instances of increased protein were recorded. Serial cell studies, performed in many cases, revealed that in general the cell count reached its highest level in two to three days and then gradually tapered off, so that at the end of approximately 10 days the spinal fluid was cytologically normal. The clinical picture, subjective and objective, cleared within a few days and did not run parallel with the lag in pleocytosis. Other laboratory data were unimportant. Figure 1 represents a composite picture of the clinical course of mumps complicated by meningo-encephalitis.

*Clinical Aspects of Acute Benign Lymphocytic Meningitis* This group includes all cases of lymphocytosis in the cerebrospinal fluid in which no specific etiology could be ascertained and the clinical course resembled cases described in the past as acute benign lymphocytic meningitis or by other synonyms. Patients were mainly young adult males of varied racial groups.

The prodromal period lasted approximately four to five days prior to meningeal signs and was manifested by respiratory, gastrointestinal or systemic symptoms. The chief complaints on admission to the hospital were headache and nuchal rigidity. Less common symptoms listed in order of frequency were vertigo, feverishness, photophobia, anorexia, lethargy and mild convulsive movements. The objective signs were nuchal rigidity (88 per cent), Kernig's sign (70 per cent), abnormal reflexes (65 per cent), Brudzinski's sign (17 per cent). There was only one case without any objective signs and his only complaints were frontal headache and slight feverishness.

The cytological study of the cerebrospinal fluid, performed within 48 hours of admission, revealed an average of 322 cells per cubic millimeter.

The lowest was 54 cells and the highest was 950 cells. Ninety to 100 per cent of all cells were lymphocytes. Upon serial studies of spinal fluid cytology it was noted that, in general, the count reached its peak within several days and gradually subsided; so that it was within normal limits in three weeks. As in mumps meningitis the clinical picture cleared rather early (usually within one week) and there was a lag in the cytological picture. Except for a proportionate increase in pressure and protein content (50 to 90 mg per 100 cc), all other studies such as the Wassermann reaction, the colloidal gold curve, bacteriological culture, glucose and chloride contents, were normal.

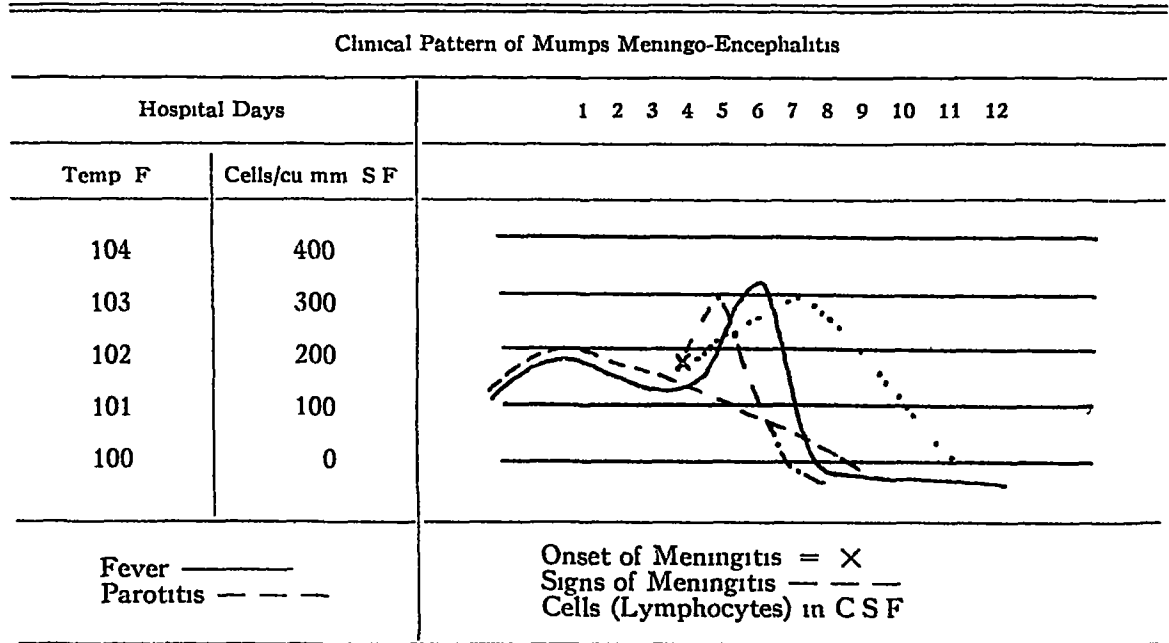


FIG 1

Ten cases were subjected to chemotherapy in the form of sulfa drugs (sulfadiazine) and seven received only palliative treatment. All ran a self-limited course and there was no appreciable difference between the sulfa-treated and non-treated groups. Patients were usually well within 10 days and the average hospital stay was one month. One case was complicated by left facial paralysis. Neither relapses nor deaths occurred in this series. Figure 2 represents a composite picture of the clinical course.

*Miscellaneous Conditions* There were seven cases of syphilis of the central nervous system with lymphocytosis in the cerebrospinal fluid. The average cell count was over 200 per cubic millimeter and the total protein was proportionately increased. Five were diagnosed as meningovascular syphilis, one as general paresis, and one was unclassified. Positive serologic reactions (Wassermann) of the blood and spinal fluid were reported in all. The colloidal gold curve revealed a mild mid-zone rise except in the case of general paresis, in which an initial elevation was observed. It was interesting to note that in three cases there was no history of a primary infection.

and, therefore, no therapy had been instituted. In the other four cases, although the primary lesion antedated the discovery of the central nervous system lesion by three to eight years, the course of treatment on the basis of history was considered inadequate in all but one.

There were four cases of tuberculous meningitis—three in children as part of a generalized miliary tuberculosis and one in an adult as the terminal event of advanced bilateral pulmonary tuberculosis. The average cell count of the initial spinal fluid study was 189 per cubic millimeter, the protein was elevated, and glucose was slightly diminished. In two cases the initial study

Clinical Pattern of Benign Lymphocytic Meningitis

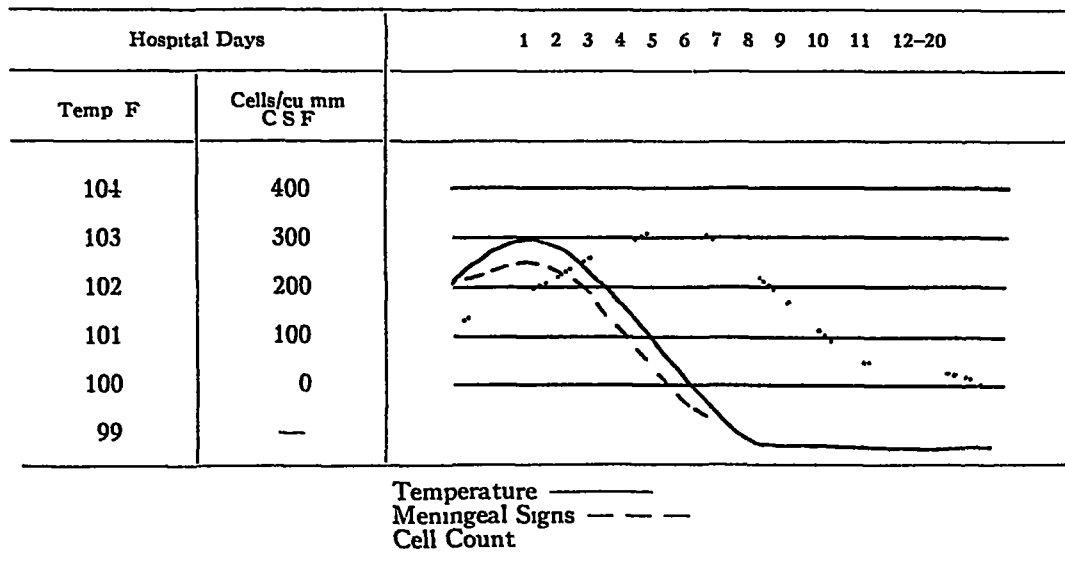


FIG 2

revealed a moderate polymorphonuclear response, but in subsequent tests there was a preponderance of lymphocytes. In two of the four cases pellicle formation and the presence of acid-fast bacilli were detected. The mortality rate was 100 per cent.

In the group of three cases due to chemical irritation, the cell count was moderate and transient. The following factors were responsible: (1) Antimeningococcus serum employed intraspinally in meningococcus meningitis; (2) Tetanus antitoxin administered intrathecally in tetanus; (3) Novocaine solution injected intraspinally for anesthetic purposes.

In the remainder of the cases, the clinical history and course, and the laboratory data aided in the solution of a specific diagnosis. Two cases fitted the pattern of acute encephalitis (virus). Two proved cases of tetanus and one case of rabies, confirmed by postmortem examination, produced a spinal fluid lymphocytosis. Trauma (1 case) and abscess of the brain (1 case) also induced sterile lymphocytic reactions (meningitis sympathica). One case was due to the Guillain-Barre syndrome (albumino-

cytological dissociation and peripheral neuritis), one was associated with severe aestivo-autumnal malaria and considered of undetermined etiology, one was part of the picture of acute infectious mononucleosis and in one case a tentative diagnosis of cerebrospinal cysticercosis<sup>1</sup> was made

### COMMENT

The incidence of mumps meningo-encephalitis in this series (3.2 per cent) is lower than expected. However, if routine lumbar punctures were performed in all cases, the rate undoubtedly would be increased. Reports in the literature vary from 0.1 per cent, based on postmortem studies by Larkin,<sup>2</sup> to 40 per cent in cases where spinal taps were performed by Finklestein<sup>3</sup> in 40 consecutive cases of mumps. Between these two extremes the figures were variable and were undoubtedly influenced by diagnostic acumen, the frequency of lumbar punctures, and the virulence of epidemics. Occasionally clinical evidence of parotid or submaxillary glandular involvement is so scanty as to make an etiological background difficult to establish. As a matter of fact, primary mumps meningitis without glandular involvement has been described<sup>4, 5, 6, 7</sup>

The neurological syndrome, which seems to follow a classical pattern in the majority of cases, is caused by the virus of mumps. Because of the rarity of deaths, pathological descriptions of tissue are uncommon. Post-mortem reports have been submitted by Larkin,<sup>2</sup> Donahue,<sup>8</sup> Urechia<sup>9</sup> and others. Edema of the surface of the brain, congestion of the pia-arachnoid and perivascular infiltration of the pia-arachnoid and the cortex by large and small mononuclear cells have been reported. Gordon<sup>10</sup> performed experimental work in 10 monkeys by means of the intracerebral injection of the virus of mumps, obtained by the passage of a gargle specimen from an uncomplicated case of mumps through a Berkefeld filter. Four animals exhibited central nervous system symptoms and died within several days. He noted lymphocytosis in the cerebrospinal fluid, degenerative changes in the nerve cells and perivascular and cortical infiltration.

Brenneman<sup>11</sup> divides the neurological syndrome of mumps into meningeal and encephalitic forms. The latter have cell counts of about 200–300 per cubic millimeter of spinal fluid and a paucity of objective signs. The former have higher cell counts and signs indicative of meningeal irritation. It is universally recognized that the prognosis is excellent and complications are infrequent. Although there were none in this group, such residuals as permanent deafness, blindness, spastic paralysis and idiocy have been listed.

In the majority of cases of cerebrospinal fluid lymphocytosis of undetermined origin, the clinical picture closely resembled that of acute lymphocytic choriomeningitis due to a virus first defined by Armstrong and Lillie<sup>12</sup> in 1934 or a condition due to an allied virus such as one isolated by McCallum, Findlay and Scott<sup>13</sup> in 1939. No facilities for identification of viruses were available to us. However, even where such facilities are present, identifica-

tion is not always possible. For example, Baird and Rivers<sup>14</sup> in 1938 were able to isolate the specific filterable virus in only 28 per cent of their clinical cases. Of interest in this zone, where both mice and mosquitoes are plentiful, are the reports of Coggeshall,<sup>15</sup> who transmitted the virus of lymphocytic choriomeningitis to a guinea pig by means of the bite of an *Aedes aegypti* mosquito, and of Armstrong,<sup>16</sup> who has demonstrated that mice are important vectors in transmission of the disease to man.

In about one-third (six cases) of our series the disease resembled aseptic meningitis described by Wallgren.<sup>17</sup> In this group the prodromal period was shorter, the disease was more benign, the cell count was lower, no residuals occurred and convalescence was more rapid.

As a clinical aid in the differential diagnosis of cases with lymphocytosis in the cerebrospinal fluid, the following classification is submitted:

- 1 *Acute lymphocytic meningitis (benign)*
  - a Acute lymphocytic choriomeningitis
  - b Lymphocytic meningitis due to allied viruses
  - c Aseptic meningitis, cause undetermined (Wallgren)

- 2 *Other diseases of virus origin*

Mumps, acute encephalitis (varieties), poliomyelitis, rabies, herpes (zoster and simplex), the common contagions, post-vaccination, lymphogranuloma venereum, infectious mononucleosis, Guillan-Barre syndrome, etc.

- 3 *Specific bacteria*

Tuberculosis, syphilis, tetanus

- 4 *Fungi and parasites (uncommon)*

Torula infection, cysticercosis, etc.

- 5 *Chemical factors (intraspinal injections)*

Serum, novocaine solution, lipiodol, etc.

- 6 *Meningitis sympathica (irritative)*

Sequela to trauma of brain, aural infection, subdural abscess, epidural abscess

## SUMMARY

1 A group of 72 cases, presenting evidence of lymphocytosis in the cerebrospinal fluid, was studied at Gorgas Hospital (Canal Zone) during an 18 month period.

2 A variety of etiological factors was detected. The two most common diseases in this series were mumps meningo-encephalitis (41.6 per cent) and acute benign lymphocytic meningitis (23.6 per cent). Syphilis, tuberculosis, chemical irritation (intrathecal injection) and other causative agents were listed.

3 The clinical patterns of mumps meningo-encephalitis and acute benign lymphocytic meningitis were presented in detail, and the early clearance of the clinical syndrome with a relative lag in spinal fluid pleocytosis was a prominent feature of both diseases.



4 A clinical classification was submitted as an aid in the differential diagnosis of lymphocytosis in cerebrospinal fluid

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#### BIBLIOGRAPHY

- 1 APPLEBAUM, I L, and WEXBERG, L E Eosinophilia in cerebrospinal fluid, Jr Am Med Assoc, 1944, cxxiv, 830-831
- 2 LARKIN, W R Mumps meningitis found at Camp Taylor Base Hospital with autopsy findings, Illinois Med Jr, 1920, xxxviii, 133
- 3 FINKLESTEIN, H Meningo-encephalitis in mumps, Jr Am Med Assoc, 1938, cxi, 17-18
- 4 STETZ and GUEZ Primary mumps meningitis, case, Tunisie méd, 1939, xxxiii, 326-329
- 5 ARMAND-DELILLE, WOLINETZ and BARBERG Primary mumps meningitis without parotid or submaxillary swelling (case), Bull Soc de pédiat de Paris, 1937, xxxv, 578-582
- 6 URECHIA, C I Meningitis of primary type, case, Bull et mém Soc méd d hôp de Paris, 1936, lii, 450-452
- 7 BERNHEIM, M, and JEANTET, R Primary parotitic meningitis (case), Lyon méd, 1934, cliv, 675-677
- 8 DONAHUE, W L Pathology of mumps encephalitis with report of fatal case, Jr Pediat, 1941, xix, 42-52
- 9 URECHIA, C I Epidemic parotitis with psychosis due to meningo-encephalitis, autopsy, Encephale, 1938, ii, 144-150
- 10 GORDON, M H Experimental production of the meningo-encephalitis of mumps, Lancet, 1927, i, 652
- 11 BRENNEMAN, J Practice of pediatrics, 1944, W F Prior Co Inc, Hagerstown, Md, ii, 5 (chapt 13)
- 12 ARMSTRONG, C, and LILLIE, R D Experimental lymphocytic choriomeningitis of monkeys and mice produced by virus encountered in studies of 1933 St Louis encephalitis epidemic, Pub Health Rep, 1934, xlix, 1019-1027
- 13 MCCALLUM, F O, FINDLAY, G M, and SCOTT, T M Pseudo-lymphocytic choriomeningitis, Brit Jr Exper Path, 1939, xx, 260-269
- 14 BAIRD, R D, and RIVERS, T M Relation of lymphocytic choriomeningitis to acute aseptic meningitis (Wallgren), Am Jr Pub Health, 1938, xxviii, 47-53
- 15 COGGESHALL, L T The transmission of lymphocytic choriomeningitis by mosquitoes, Science, 1939, lxxix, 515
- 16 ARMSTRONG, C Some recent research in the field of neurotropic viruses with especial reference to lymphocytic choriomeningitis and herpes simplex, Mil Surg, 1942, xci, 129-146
- 17 WALLGREN, A An unusual form of epidemic meningitis (Meningitis aseptica acuta), Wien Arch f inn Med, 1926, xii, 297-312

## NEUROSES IN THE COMBAT ZONE\*

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LITTLE did any of us believe, four years ago, that our nation, morally decent and peaceloving, could be developed into the greatest military power in the history of mankind! Little did we realize that we could mobilize our manpower and production to provide the necessary material to prosecute this global war. We not only succeeded in preventing enemy invasion of our own shores but helped turn the tide for our beleaguered allies who were facing impending disaster. A few years ago we were a smugly complacent pacifistic democracy, comfortably entrenched in a false feeling of security due to what we thought was geographical isolation. Today, the problems of the world are *our* problems and we have succeeded in making the necessary emotional and mental adjustments to include the problems of the down-trodden and lesser world powers with our own. In part, our interest has expanded because today we find American youth fighting shoulder to shoulder with the people of almost every land in all corners of the globe, and we are helping them in material ways to rid the world of the evil forces which would have destroyed our civilization. Even though we cannot share the ardent hatred with those countries who have been ravished by a designing and cruel foe, we can say that America has developed a potent philosophy—our Good Neighbor policy—which has carried us so far toward the victorious termination of this great world conflict. We must admit that both our soldiers and our people lack that passionate hatred for our enemy because we have not experienced, as a nation, the deep-seated bitterness and resentment toward a ruthless enemy who has wantonly destroyed the civilian population and homes of our allies. Pearl Harbor and reported Jap and Nazi atrocities kindle such a flame, we respond temporarily in an emotional way, but the flame dies down because our American homes are intact and our families safe from enemy assault and the war is reaching a successful conclusion. To preserve the emotional armament necessary to win an early peace we must stimulate a political, moral and religious fervor—a high morale. The rôle of a high morale will be discussed at greater length.

Medicine has shared very materially in the success of our tremendous effort. We contributed our part, both in the selection of the manpower fit to fight, and in the care of those who became casualties. The appalling statistics of physical and mental unfitness, revealed by our Selective Service induction examinations, startled the nation, but not the profession. With a reasonably careful screen the great proportion of the physically and mentally unfit were rejected. During the ensuing months our men passed

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through reception and training centers and were assigned to units for further training, where many more men were found unequipped for service and were discharged. In spite of these repeated screens and surveys, however, many thousands of men who were poorly equipped for combat overseas, escaped detection. The omissions and imperfections of our methods of examination are partly to blame for this additional burden on the Medical Department. Further difficulty results from our inability properly to evaluate all of the factors that make up the highly complex human mechanism. We still know of no yardstick of measurement that will foretell the reaction of any individual under the abnormal stress and strain of war. The experiences gained in World War I and during the 20 years that followed have added greatly to our knowledge and understanding of the human mechanism, but we are still far removed from that complete understanding and appreciation of the intricacies and vagaries of human behavior.

We recognize, therefore, that many individuals reach the combat zone who are basically poorly equipped and in whom antecedent neurotic maladaptation is latent. Those, with similar predisposition, who developed disabling neuroses when first exposed to military life or during the early training period in the states, should be considered as suffering from a relatively severe neuropathic disturbance. In these people the environment and stress are little more severe than those experienced in civilian life. They are of little military value and early separation from the service may permit of a reasonable adjustment at a former civilian level. Those who develop "gangplank fever" or who break beyond the three mile zone or survive the ocean voyage only to "crack up" after landing on friendly foreign shores still belong to the same group in whom preexisting psychological traumata are inherent and determining factors. The clinical pictures, prognosis and treatment are almost identical with those observed in civilian practice. Experience has proved that attempted rehabilitation of these individuals, with the hope of restoration to a duty status with troops, is futile.

Moving forward toward the combat area we find still another group that develops anxiety states provoked in a great measure by wild stories and exaggerated rumors of fellow soldiers. This, together with a tension state and associated loss of sleep, is sufficient to produce a mental upheaval. These cases undoubtedly have scars of former mental disruptions, but we found they could be made to live with their neurosis if assigned to units in the rear and they were not lost to the army.

Our next group of mental casualties occurs in the area immediately behind combat activity. It is reasonable to assume that any soldier who has succeeded in masking his neurotic pattern up to actual entrance into combat is not suffering from a malignant disorder.

At this point we shall consider the many provocative factors that are a part of the overall picture, influencing the lives of even the normal individuals who find themselves in this abnormal setting. Having served on only one

active front I choose to describe the tangible factors that were evident in our theatre, namely, the S W P A

Ernie Pyle, Major Ralph Ingersoll, Captain Spiegel, Captain Appel, Lieutenant Colonel Grinker, Commander Braceland, Colonel Porter and many others have masterfully portrayed the picture as they saw it in the African, Italian and European theatres. Their reports should be read to provide the background for better understanding of the problem and the reaction of our soldiers in combat.

In tropical warfare we found environmental factors that are not obvious in other theatres of war. It is felt that they add materially to the development of neuroses among our troops. The heat of these islands, although high, is not unbearable. The humidity, approaching saturation for months on end, is devastating. A noticeable weight loss is evident after a few months in the tropics. Nearly every soldier loses an average of 10 per cent of his normal body weight. This is not due altogether to poor food or food deficiencies. Initially, all troops practice rigid salt discipline. As the months roll by one becomes accustomed to excessive sweating and a proper salt balance is almost universally neglected. A chronic low blood chloride level may account for what has been described as a tropical neurasthenia. It is firmly believed that a marked weight loss with concomitant reduction in general physical stamina is a predisposing cause for many neurasthenic complaints. Frequently a mild gastrointestinal upset with diarrhea may be the forerunner of an acute mental break. One point universally agreed upon by all who spent a year or more on the tropical islands was that a chronic state of fatigue developed in direct proportion to the duration of service of troops in these areas.

Extended effort for a short time during actual combat brings about exhaustion and favors the development of neuroses of combat origin. We who served there knew of many normal men who finally reached their elastic limit, both mentally and physically, and cracked under the strain. This opinion is shared by all medical officers and psychiatrists who served with combat troops.

I dare say that if we were all to be carefully psychoanalyzed, previous neuropathic traumata might be uncovered in all normal people. To conclude that these early experiences finally come to the fore and play an active part in crushing the ego strength and defense is obviously absurd<sup>1</sup>. We know that the fatigue and exhaustion and the stark realism and gruesome wanton destruction, which surround the fighting man, will cause a gradual collapse and regression of the normal ego.

The tropical islands present other problems. There are no safe rear areas for rest or refuge. Earlier in the war when the Jap had air superiority and control of the sea lanes, bombing, strafing and naval guns added to the discomfort and anxiety of combatant as well as noncombatant troops alike. There was no escape. The repeated mental insult of constant shelling finally dulls the normal sensorium, and men became automatons. There is a sense

of unreality about these attacks. Many admit of retrograde amnesia as though there were a mild concussion following the explosion of bombs and heavy shells. This was more common among the men who were unable to retaliate against the enemy attack. The men who manned the anti-aircraft guns, the machine gunner, and even the rifle man, suffered less in these attacks. They could release and expend the pent-up emotions and burn up, through activity, the glycogen mobilized by excessive adrenal activity. They were less tense when it was over. By comparison, the unarmed inactive soldier who sought shelter in a foxhole or slit trench showed a greater pallor and less facial expression, a greater paucity of free associated movement, some tremor and all the signs of excessive adrenalinization, and a thalamic syndrome. It took him longer to regain his normal poise. After the attack there was a compensatory hyperactivity and loquaciousness sometimes bordering on an hysterical outburst of yelling and swearing when the "all clear" signal was given. It should be obvious that daily repetition of such assault and mental insult would undermine even the most stalwart unemotional type. It became the duty of every company officer to observe the after effect of these attacks upon the members of his command. Two observations were significant. Increased hyperactivity and overacting, with almost a false bravado, although compensatory, was watched with suspicion. Some of these men became aggressive and manic-like with subsequent similar experiences. The soldier who became irritable, depressed and seclusive, and who failed to carry out or to obey orders for the first time, and who was known to go without sleep, was sent to the medical officer for advice and medication. Rationalization of his fear, reassurance, and a mild hypnotic most often brought about a rapid restoration. He was watched very carefully during subsequent enemy attacks and if he demonstrated further regression he was hospitalized. It was rare to find men who succumbed to single enemy assaults. Repeated exposures in a trying physical environment in people who were exhausted from physical hardship, or convalescent from physical illness, produced ego regression and disintegration. The rôle of the combat team psychiatrist in evaluating the condition of the troops and counselling with the line officers cannot be overemphasized.

In actual jungle warfare unbelievable physical hardships were encountered which added materially to production of battle reactions. Mud was knee-deep, torrential rains, or numerous showers and steaming jungle with impenetrable thick undergrowth, were the typical scenes of the man-hunt. There was no front line. The enemy hid in trees and attacked from all directions. Death lurked around every bend along the vine-covered trails. Men stalked the enemy as a hunter does an animal. The Yellow "animal" was as treacherous as a mountain lion. Raiding parties or squads, the small family group, comprised our tactical units. This vicious, tricky, fanatical foe fought with a frenzy and fury seen only in wounded wild animals when cornered.

There are many other factors peculiar to all theatres of actual combat

that must be mentioned fully to appreciate the underlying mechanism of combat area neuroses. Some are instinctive and inherent, whereas others are acquired, such as poor orientation, inadequate training, poor leadership and lowered morale.

Little need be said about fear in this discussion. The average soldier knows that fear is a normal reaction. He has been told that every normal individual is afraid, and that it is not disgraceful, in fact, it is a desirable attribute. He receives a simple explanation of the biochemical changes produced by fear, and how the body mobilizes adrenalin and glycogen, and how the organism goes on the alert as the result of increased nervous tension. He is told how to master that fear. The primitive herd instinct is explained to him. He understands why he prefers to fight alongside of men whom he knows and trusts. He is taught how to meet the enemy when he is alone, on his own. He knows the enemy is also afraid and he is schooled in how to outguess and outwit his adversary.

Because we have been a nonbelligerent people, and because we lack the fanaticism, hatred, and primitive destructive drive of the Nazi and Jap, it has been necessary to indoctrinate our soldiers with a bitterness and resentment, and to try to stimulate a hatred for the enemy based upon the atrocities committed on our soldiers and our allies by our ruthless foe. The morale of a fighting force is probably more important than any single factor in the production of neuroses in the combat area. Following are some of the more important factors that affect the morale of a unit adversely.

Competent leadership is most important. There is no place in our Army for an officer who cannot lead his men, fight for his outfit to get better mail service, more amenities and better food. He must share in the hardships and deal firmly but fairly with his command. He must inspire confidence and loyalty in the outfit. He must make his men believe that they have the best outfit in the whole theatre, and his praise for things well done helps more than criticism for the mistakes they make. He quarterbackes the team and runs the plays. Such an officer will carry his group through many a tight place and they will have very few mental casualties. If he is the first to jump into a slit trench and get the jitters, a mass panic may result. Unfortunately, anxiety and panic are highly contagious emotions.

The long inactive periods, awaiting action, the monotony of isolation in a restricted sphere, the lack of mail, or worse still, the receipt of letters from home which worry the soldier, particularly those which describe illness, financial or domestic troubles, are most demoralizing. Letters of complaint, and description of strikes at home, fabulous incomes of the friends who are not in the service, all create resentment and bitterness and make the soldier say, "What the hell am I fighting for?"

Prolonged overseas service with slow promotion, a lack of social and sexual outlet, inadequate entertainment and recreational opportunity have an accumulative effect and establish an insidious background for a real mental "blow-up." We see a progressive irritability and restlessness at first, later a

listlessness, and lack of initiative approaching apathy When the soldier stops griping there is trouble ahead

All of these more intangible, yet important phases of a lowered morale, are commensurate with the time the soldier spends overseas I am doubtful if we can create the necessary spark by any method of indoctrination unless it is combined with a prolonged rest or furlough in some civilized and normal community far removed from battle—preferably home If it were practical it would be most desirable to remove the entire team as a unit

The feeling of insecurity provoked by many of the above factors establishes a fertile soil for the superimposed ego regression Psychoneurotic escape patterns naturally develop in those who succumb to these intrinsic and extrinsic stimuli

### CONCLUSIONS

1 As a nation, involved in a global war, we find ourselves fighting *for* others rather than *against* an enemy We lack the fanaticism, hatred and primitive destructive drive found among those countries either bent on the acquisition of territory and the pillage and destruction of their enemy, or those nations with their back against the wall trying to preserve their homes and prevent the rape and murder of their beloved ones

2 Our fighting men, as a class more intellectual, consequently more sensitive, and subject to emotional lability, are fighting many thousands of miles from home under conditions of great physical hardship, because of a *sense of duty* This altruistic motive would be insufficient for a less intelligent people In spite of all this we have no greater incidence of neuropsychiatric disability than our allies or enemy We simply recognize and admit their existence and treat them

3 Acute emotional breaks occur under combat conditions and are the direct result of fatigue, exhaustion, and the strain in combat Normal people are victimized Early treatment in the combat areas restores most of these people in a matter of days to a full duty status The fact that so few cases of this type recur, unless resubjected to similar prolonged engagements under the same conditions, is indicative of a benign illness The animal organism has suffered both a physical and mental depletion of energy that renders it helpless Temporarily, these men have reached their elastic limit of endurance and collapse Rapid revitalization physically and artificially induced mental rest brings about a return of a normally functioning unit The prognosis is excellent This condition does not merit the application of a psychiatrically stigmatizing name or term Even those patients who pass through our chain of evacuation to the zone of interior because of a more prolonged convalescence continue to show improvement as their boat approaches our American shore

4. Continued improvement and many recoveries take place in our convalescent hospitals and reconditioning centers here at home We can be extremely optimistic about these cases and can even offer a good prognosis

for most of the less malignant psychoneuroses that show evident preinduction signs of psychological traumas. From experience, we are convinced that we are seeing many more recoveries among our psychoneurotic casualties from overseas than are to be found among the same group of more deep-seated maladjusted individuals who never went abroad. The latter group are more malignant and refractory toward treatment.

5 The increased incidence of psychiatric disorders is often indicative of lowered morale. Factors that lower morale have been discussed.

6 Preventive psychiatry, proper orientation and indoctrination before combat are essential to the maintenance of a high morale and a decrease in the incidence of psychiatric disabilities. The importance of having psychiatric guidance in combat areas is obvious. The rôle of the psychiatrist as a staff officer of the tactical commander must be emphasized.

7 I am convinced we have the finest fighting force, the best informed, the most intelligent, and, therefore, the greatest military power on earth. What we have lacked in zeal and fanaticism, factors which, in the light of the enemy wanton waste of human life, seem stupid, we have gained by intelligent planning and tactical execution, thus conserving the lives of our fighting men and preserving our American way of life.



# NEUROPSYCHIATRIC COMPLICATIONS FOLLOWING SPINAL ANESTHESIA \*

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THE advantages of spinal anesthesia under certain restrictions are so obvious and the results obtained from its use so excellent that one can appreciate the popularity of this valuable anesthetic measure. However, from time to time, there have appeared in the literature reports of patients who have developed neurological complications occurring immediately after or remotely following the administration of a spinal anesthetic. The statements in the literature are extremely contradictory as to the frequency with which such nervous sequelae occur. Emmett<sup>1</sup> reports he had no neurological sequelae in 1415 cases, and Foss and Schwalm<sup>2</sup> state that in 3,000 cases they have never seen the slightest evidence of peripheral neuritis or sensory or motor disturbances. They quote Pemberton to the same effect. On the other hand, White-Morquecho,<sup>3</sup> Peirson and Twomey,<sup>4</sup> Ferguson and Watkins,<sup>5</sup> Hammes,<sup>6</sup> Kammon and Baker,<sup>7</sup> Lindemulder,<sup>8</sup> Hyslop,<sup>9</sup> Brock, Bell and Davison<sup>10</sup> and others have recorded definite instances of neural diseases following the administration of a spinal anesthetic. Hyslop gives 0.5 per cent as the incidence of sequelae in the central nervous system. Jarmen<sup>11</sup> gives the incidence of paralysis as one in 10,000 cases. Loeser<sup>12</sup> believes that an inflammatory syndrome affecting isolated peripheral nerves is more frequent than is realized. He reports five cases in one year. Egorova<sup>13</sup> reports 128 cases of which involvement of cranial nerves took place in 3.2 per cent, sphincter disturbances in 13.8 per cent, diminution or loss of tendon reflexes in 15.6 per cent, and paresis of the lower extremities in 4.6 per cent. These complications were not associated with preexisting nervous lesions. A review of the literature and the personal experiences recorded by Critchley,<sup>14</sup> and Light and his colleagues<sup>15</sup> suggest that neurological complications occur much more frequently than is commonly supposed. Nervous complications of the most varied types may follow the use of spinal anesthesia. Clinically, the neurological complications display great diversity and range from cranial nerve palsies and peripheral mononeuritis to transverse myelitis and encephalomyelitis. Among isolated cranial nerve paralyses, unilateral or bilateral abducens palsy is most frequent. Involvement of the optic, oculomotor, trigeminal, facial, auditory and hypoglossal nerve has also been reported. Lesions of the cauda equina, myelitis, myeloradiculitis, aseptic meningitis and encephalomyelitis have been recorded. Thus, almost

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any part of the central nervous system may be affected. A survey of the literature makes it apparent that a wide variety of neurological complications, either immediate or remote, mild or severe, temporary or permanent, may follow spinal anesthesia.

In the past few years we have been concerned with a number of neurologic and psychiatric problems in which the question of a relationship to a previously administered spinal anesthetic was pertinent. We are reporting six personally observed instances of neuropsychiatric complications following spinal anesthesia. We are also describing a case of metastatic spinal cord neoplasm which came to light following spinal anesthesia in which the anesthetic agent was for a while suspected as being the cause of the myelitic syndrome. These cases are presented not as a disparagement of a very valuable, if not indispensable, form of anesthesia, but with the intent to emphasize the necessity of looking for and recognizing complications, and, if possible, preventing them.

#### CASE REPORTS

*Case 1* H McK., West Jersey Homeopathic Hospital. Syndrome of cauda equina neuritis, conus medullaris and lumbosacral cord involvement immediately after pontocaine spinal anesthesia. Poor recovery after four years.

*History* The patient, a male of 48 years, was admitted to the Hospital and was operated on for a ruptured duodenal ulcer on November 6, 1940, under spinal anesthesia. A solution of 15 cc of pontocaine hydrochloride plus 15 cc of glucose solution was injected in the third lumbar interspace. The administration of the anesthesia and operation were uneventful. The next day he complained of lack of sensation in his lower extremities. He had incontinence of urine and feces. On examination he was found to have a flaccid crural paraplegia with absence of deep tendon reflexes. His physician found the patient had a loss of all sensory perception up to a point above the symphysis pubis.

*Examination* On February 19, 1941 the patient was examined by one of us (H E Y). The cranial nerves were normal. The muscular power, reflex activity, and sensation of the upper extremities and trunk were normal. A flaccid crural paraplegia existed with bilateral foot drop. The patient was able to execute feeble contractions of the sartorius and quadriceps femoris groups of the right thigh. However, the remaining muscle groups, especially the hamstring muscles, were completely paralyzed. There was early atrophy of the involved muscles. The deep tendon reflexes of the lower extremities were absent. The abdominal reflexes were present and equal. The cremasteric and gluteal reflexes were absent. Sensory examination revealed a radicular type of sensory loss in the lower extremities and complete anesthesia of the genitalia and saddle area. There was anesthesia in the radicular zones innervated by roots L-1 to S-5 inclusive on the right. There was hypalgesia and thermhypesthesia in the radicular zones L-1 to L-3 inclusive on the right. Vibratory perception was lost up to the level of the first lumbar dermatome segment. Position sense was lost in the toes of both feet. The anal sphincter was atonic. There was an indwelling urinary catheter in situ with an attached tidal drainage apparatus. Clinically the patient presented a syndrome of severe cauda equina neuritis with involvement of the conus medullaris and lumbosacral cord.

*Laboratory Data* Because the patient had been a painter for 30 years the possibility of lead intoxication was investigated. Repeated blood cytology studies revealed normal findings. Red blood cell stippling was never discovered. Blood and

spinal fluid serologic tests were negative. Roentgenologic studies of the long bones, the sacral spine and the pelvis were all negative. Rectal examination and sigmoidoscopy yielded negative findings. Analysis of blood for lead gave findings which suggested that the patient had a "mild active phase of partially delayed chronic plumbism." The lumbar puncture, done on November 20, 1940, yielded clear, colorless fluid under an initial pressure of 160 mm of water. The spinal dynamics were normal. The total protein content of the spinal fluid was not determined.

*Course* Six months after his operation the patient was again examined. He could now control urination by voluntary effort. He could perceive the sensation of a full bladder. When he got this sensation he could, by compressing his abdominal wall, initiate urination. He also had a return of subjective sensation in his rectum and by straining could effect defecation. He still had a flaccid paraplegia which was complete except for the ability to execute motor movements of a slight degree with the muscles of his right thigh. Bilateral foot drop persisted. He complained of sharp, shooting pains in both legs and, occasionally, in his genitalia. He had developed early contractures of both knee joints. There was atrophy of the posterior thigh muscles and gluteal muscles, more marked on the left side. The deep tendon reflexes were still absent in the lower extremities. The sensory disturbances found at the time of the first examination still persisted. The patient has not been seen since the last examination, but a verbal report recently received states that the man still has a crural paraplegia, more than four years after its inception.

*Discussion* The question of plumbism as a possible etiology of the sudden paralytic syndrome was raised by a few of the examiners. However, from the onset of symptoms, almost immediately after spinal anesthesia, which we know can be occasionally followed by neurological complications, we may conclude that the cauda equina neuritis and conus medullaris involvement were directly caused by the toxic action of the anesthetic agent used. The possibility of a preexisting cauda equina neoplasm, primary or secondary, which may have come to light coincidentally at the time of his operation was ruled out by proper laboratory studies. The course of the neurologic picture in this patient emphasizes the poor prognosis which we may expect in some of the cases of post-spinal anesthesia myeloradiculitis.

*Case 2* C T B, Jefferson Hospital. Syndrome of conus medullaris and cauda equina involvement immediately after metycaine spinal anesthesia. Poor recovery after two years.

*History* The patient, a female of 53 years, was admitted to the Hospital three months after she developed symptoms of numbness of the medial aspects of the buttocks and perineum together with incontinence of feces and frequency of urination. These symptoms had their inception immediately after an operation for cystocele and rectocele under metycaine spinal anesthesia in June, 1942. The dosage of anesthetic agent used is unknown. Immediately after the operation she had to be catheterized for 18 days and she was incontinent of her feces. Since then she has had urgency of urination, urinary dribbling, "pains" in her vagina, and fecal incontinence.

*Examination* On September 23, 1942 the neurological examination disclosed impairment of sensation (pin prick and temperature) over the perianal region, over the perineum, and over the posterior aspect of the upper thighs and buttocks, conforming to dermatome distribution of roots S-3 to S-5 inclusive. This saddle area sensory disturbance was more marked on the right side. Rectal incontinence was present. Clinically, the patient presented a syndrome of cauda equina and conus medullaris involvement.

*Laboratory Data* On September 27, 1942 the rectal and proctoscopic examinations disclosed fair tone of the anal sphincters and nothing abnormal in the rectum. Cystoscopic examination at this time revealed a markedly hypertrophied and trabeculated bladder with evidence of some loss of function of the external sphincter. Cysto-

metric examination revealed a hypertonic rather than a hypotonic bladder. Roentgenologic studies of the lumbosacral spine were negative. Examination of the urinary tract by intravenous urography was negative. Blood cytologic studies and urinalysis yielded normal findings. No lumbar puncture was done, hence no spinal fluid examination was made.

*Course* It was thought the patient had a cauda equina syndrome involving the distal sacral roots. In view of the precipitous onset following spinal anesthesia, the disturbance was considered toxic in origin. The patient was seen for reexamination on March 24, 1943. She complained most of severe burning pain in the vagina which she stated was present since operation. Urinary and fecal incontinence were still present as was the numbness in the saddle area. Her bowels failed to move without a laxative. More recently, she had noticed a heaviness of her feet and difficulty in walking. Examination at this time revealed a weakness of dorsiflexion of the left foot and an absent ankle jerk on that side. The sensory impairment found on her previous examination was less definite. She now displayed a great deal of emotional instability. Her condition was regarded as being psychogenic in origin and she was given electrocerebral shock treatment. With three such treatments no improvement was noted. The patient was readmitted to the Hospital on November 30, 1943 with the previous complaints. Neurological examination again revealed loss of pain and temperature sensation along the inner aspects of the thighs and around the anus (radicular zones S-3 to S-5 inclusive). This finding was unassociated with any muscle atrophy. Proctoscopic and cystometric examinations demonstrated an anal sphincter of normal tone and a hypertonic bladder respectively. Lumbar puncture yielded clear, colorless fluid under an initial pressure of 130 mm of water. The spinal fluid dynamics were normal. The blood and spinal fluid Wassermann and Kahn reactions were negative. The spinal fluid total protein was 31 mg per cent. The patient continued unimproved.

*Discussion* The immediate onset of bowel and bladder sphincter disturbance following spinal anesthesia makes the conclusion inescapable in this case, that the patient experienced a toxic lesion of the conus medullaris and cauda equina. The peculiar sphincteric disturbances are probably accountable by a conus lesion, whereas her subjective and objective sensory disturbances indicate an element of cauda equina neuritis. As in many cases of a chronic, incapacitating illness, this patient developed psychogenic symptoms which at one time dominated her clinical picture and gave the misleading impression that the entire clinical syndrome might be psychogenic in nature. The possibility of a cauda equina or conus neoplasm was ruled out.

*Case 3* L. B., Jefferson Hospital. Syndrome of incomplete thoracic transverse myelitis with spastic crural paralysis immediately after procaine spinal anesthesia. No recovery after one year.

*History* The patient, a male aged 57 years, was admitted to the Hospital four months after he developed symptoms of a spastic crural paraplegia. On October 5, 1943 he had been operated on for a left inguinal hernia at the Cooper Hospital under spinal anesthesia. A solution of 150 mg of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. Two days after the operation he complained of numbness which descended from the hips to the toes. He also noticed an inability to move his legs which became progressively worse. After his discharge from that hospital he soon discovered he could not move his legs at all. The numbness persisted. No bowel or bladder dysfunction developed. On February 18, 1944 the patient was admitted to the Jefferson Hospital. He had a spastic crural paraplegia.

*Examination* The cranial nerves were normal. The muscular power, reflex activity and sensation of the upper extremities were normal. He had a marked extensor spasticity of the legs. He could not flex the legs and could only feebly flex

the feet. He was unable to walk except with crutches. The patellar and Achilles tendon reflexes were overactive. He had bilateral ankle clonus but no pathological reflexes. Pain, temperature and vibratory sensation was lost below the fourth thoracic dermatome segment on the right and below the fifth thoracic dermatome segment on the left. Position sense was impaired in the toes of both feet. The saddle area was involved in the sensory loss.

*Laboratory Data* Lumbar puncture at the Cooper Hospital on November 29, 1943 yielded clear, colorless fluid under an initial pressure of 148 mm of water. The spinal fluid dynamics were normal. The Pandy test was negative. The spinal fluid cell count revealed two red blood cells and one white cell per cu mm. The blood and spinal fluid Wassermann reactions were negative. At Jefferson Hospital roentgenologic studies of the cervicothoracic and lumbosacral spine were negative. Repeated lumbar punctures failed to give any evidence of fluid block. The spinal fluid total protein was 70 mg per cent. The blood cytology, blood chemistry and urinalysis studies were negative. The blood and spinal fluid serological tests were negative.

*Course* There was no improvement or progression in the patient's clinical picture during the year following its inception.

*Discussion* The patient developed a spastic paralysis which appeared immediately after spinal anesthesia. He stated his symptoms progressed for five to 10 days and then became stationary. At the time of this report he had an incomplete transverse myelitic syndrome at the T-4 and T-5 spinal cord level. Possible spinal cord neoplasm, syphilitic myelitis and intramedullary hemorrhage have been excluded. The obvious diagnosis remaining is that of spinal anesthesia toxic myelitis.

*Case 4* M S, Jefferson Hospital. Syndrome of primary lateral sclerosis with spastic crural paraparesis immediately following procaine spinal anesthesia. No recovery after one year.

*History* The patient, a female of 48 years, was admitted to the Hospital two months after she developed symptoms of a spastic crural paraparesis. On October 14, 1943 she had been operated upon for a left inguinal hernia at the Cooper Hospital, under spinal anesthesia. A solution of 120 mg of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. Immediately after the operation she experienced frequency of urination which persisted for a week, then cleared. At the same time her legs felt weak and her calves felt cramped. When she attempted to get out of bed her legs felt weak and stiff. The weakness and stiffness persisted and increased in degree. On January 24, 1944 she was admitted to the Jefferson Hospital.

*Examination* The cranial nerves were normal. The muscular power and reflex activity of the upper extremities and trunk were normal. There was a marked extensor spasticity of her legs, more marked in the left leg. She was barely able to walk because of the spastic paraparesis. The deep tendon reflexes were hyperactive in the lower extremities and there were bilateral Chaddock's and Babinski's signs present. The abdominal reflexes were absent. All sensory modalities were preserved.

*Laboratory Data* Lumbar puncture yielded clear, colorless fluid under an initial pressure of 110 mm of water. Spinal fluid dynamics were normal. One cell per cu mm was found. The spinal fluid total protein was 46 mg per cent. The blood and spinal fluid Wassermann and Kahn reactions were negative. Blood cytology, chemistry studies and urinalysis were negative. Roentgenograms of the lumbosacral spine and pelvis were normal. To rule out the possibility of an existing spinal cord tumor spinal lipidol myelography was performed. This study failed to reveal any spinal canal block.

*Course* One year after the onset of her spastic paraparesis she showed no recovery. Her disability was as marked as when she was first examined.

*Discussion* There can be no doubt that the patient experienced a post-spinal anesthetic toxic myelopathy. The interesting feature is the production of a clinical syndrome of a primary lateral sclerosis with only pyramidal tract involvement.

*Case 5* A. K., Jefferson Hospital. Onset of hysterical "paralysis" of lower extremities one year after spinal anesthesia. Experience during spinal anesthesia utilized in the hysterical conversion mechanism. Good recovery with sodium amytal narcosis.

*History* The patient, a female aged 31 years, was operated upon April 26, 1943 for an acute gangrenous appendicitis and a papillary cystadenocarcinoma of the right ovary, under continuous spinal anesthesia. The initial dose of the anesthetic was 100 mg of novocaine. In all, she received 450 mg of this drug. The administration of the anesthesia and the operation were uneventful. She was readmitted to the Hospital on August 9, 1944 with the history that in February, 1944 she developed an inability to walk. She became extremely apprehensive, developed pain over the precordium and was possessed with the fear that she would never be able to walk again.

*Examination* The patient was reluctant to get out of bed to walk. When she did, her gait was a bizarre shuffling, twisting one which has been described as hysterical atasia abasia. The motor power in all her extremities was preserved. The deep tendon reflex activity was normal in her lower extremities. All the sensory modalities were preserved. Emotional instability was marked.

*Laboratory Data* The blood cytologic and urine studies were negative. The blood Wassermann reaction was negative. The electrocardiographic tracings were normal. Roentgenograms of the lumbosacral spine revealed no abnormalities.

*Course* When the history was presented the possibility of a delayed spinal anesthesia toxic myelitis was entertained. However, the neuropsychiatric examination made it obvious that we were dealing with a case of anxiety neurosis in which the patient had developed a hysterical "crural paraparesis." In talks with her it became clear that she had unconsciously utilized her spinal anesthesia experience in the past in the psychogenic formation of her present gait disability. Sodium amytal narcosis was utilized in the psychiatric treatment of her condition. One narcosis session was sufficient to clear her hysterical gait disturbance. With further psychotherapy the patient recovered from this disability.

*Course* The case is interesting in that it indicates how an emotionally unstable individual may utilize the experience under spinal anesthesia later to develop a hysterical "paralysis" of the lower extremities.

*Case 6* H. T., Jefferson Hospital. Onset of hysterical "spastic paresis" of lower extremities immediately after spinal anesthesia. Good recovery with electro-cerebral shock therapy.

*History* The patient, a female aged 32 years, was operated upon August 14, 1943 in the Cooper Hospital for a chronic inflammatory pelvic condition under spinal anesthesia. A solution of 10 mg of pontocaine dissolved in 10 per cent glucose was injected in the third lumbar interspace. Two days after the operation she developed a sensation that the toes of her feet were trying to curl under. Shortly thereafter her legs became stiff. When she tried to walk her legs were stiff and weak. At times she developed chronic tremors of both lower extremities. The spasticity of her legs seemed to increase and the episodes of clonic tremors of her extremities occurred more frequently. She had innumerable other somatic symptoms such as numbness of her feet, itching sensations, tachycardia and insomnia. She was admitted to the Jefferson Hospital on March 28, 1944.

*Examination* The patient walked with a stiff-legged mincing gait which was certainly not the gait of a spastic paraparesis. Motor activity was normal in all muscle groups. The reflex activity was increased in all the extremities, but equal. There were no pathological reflexes. All sensory modalities were preserved. On

numerous occasions she developed clonic tremors of both lower extremities while in bed. The patient was very tense and apprehensive. It was felt she was suffering from hysteria and her gait difficulties were in the nature of conversion phenomena.

*Laboratory Data* Blood cytology and urine studies were negative. The blood Wassermann reaction was negative. Because of her acute anxiety state no spinal tap was done.

*Course* The patient was suffering from a severe psychoneurosis precipitated by a complicated psychosexual conflict. Her conversion syndrome was no doubt conditioned by her subjective experiences under spinal anesthesia. Sodium amytal narcosis therapy was attempted but did not achieve desired results. Her incapacitation was so great and her conflict so fixed that she was subjected to electrocerebral shock therapy. After five such treatments her syndrome cleared. With psychotherapy she has maintained her improvement.

*Discussion* This case is similar to the preceding one except that the conversion occurred almost immediately after the spinal anesthesia. Again, a patient with psychogenic illness conditioned her hysterical gait upon her previous subjective experience with spinal anesthesia.

*Case 7* E. M., Jefferson Hospital. Syndrome of radicular pain and rapid progression of a transverse myelitis a week following procaine spinal anesthesia. Suspicion of toxic anesthetic myeloradiculitis. Real etiology metastatic bronchogenic carcinoma to coverings of cord and brain.

*History* The patient, a female of 53 years, was admitted to the Jefferson Hospital three months after the removal of her gall-bladder at the Cooper Hospital. She was operated on under spinal anesthesia. A solution of 150 mg of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. After the operation she developed sharp pains in the back and right extremities. Two weeks later she noticed numbness of the legs. At about this time she developed weakness of the lower extremities. The numb sensation ascended to the lumbar region and she became incontinent of urine. With the onset of the paralysis of her legs she had burning and tight constricting sensations around her upper abdomen. She was returned to Cooper Hospital and finally transferred to Jefferson Hospital. Additional history was then obtained that the patient had severe back pain which appeared at the same time as her right upper quadrant pain prior to her operation. The suspicion was entertained by her physician and surgeon that she had experienced a myelitic syndrome due to the toxic action of the spinal anesthesia.

*Examination* The patient was sensorially clouded and her responses slow and confused. There was marked weakness of the muscles of the arms and hands. She had a complete flaccid paralysis of her legs with absence of all deep tendon reflexes. There was complete loss of all sensation below the level of the fourth thoracic dermatome level. Position sense was absent in the toes of both feet. She was incontinent of urine.

*Laboratory Data* Blood cytology studies revealed a severe secondary anemia. The blood calcium level was 10.2 mg per cent and phosphate was 2.2 mg per cent. Spinal puncture yielded a small amount of gelatinous xanthochromic fluid which clotted on standing. The initial pressure was 40 mm of water. Spinal fluid dynamics indicated an almost complete block. Roentgenograms of the lumbosacral spine were negative. Films of the skull showed the presence of several metastases to the calvarium. Films of the right femur revealed the presence of a pathologic fracture through the upper third of the femoral shaft.

*Course* On review of her history and neurological findings an extramedullary metastatic malignancy was immediately suspected. The history of radicular pain antecedent to her spinal anesthesia, the rapid clinical progression of her myelitic syn-

drome, and the debility of the patient indicated a rapidly extending lesion such as a malignancy to the coverings of the spinal cord. The mental picture of the patient also directed attention to the possibility of metastasis to the brain. The patient became stuporous and died four days after her admission.

*Necropsy* The important finding at necropsy was a bronchogenic carcinoma of the right upper lobe of the lung. There were metastases to the mediastinal, lower abdominal and pelvic lymph nodes, to the liver, kidneys, fourth and eighth thoracic vertebrae, left ilium, right femur and skull. Neuropathological study revealed a metastatic lesion in the left frontal lobe of the brain and the dura of the spinal cord was infiltrated with a hard firm neoplastic mass. This metastatic neoplastic dural infiltration was most marked at the level of the ninth thoracic spinal cord segment.

*Discussion* When the patient was observed by us the diagnosis of a metastatic malignancy to the spinal canal was not difficult to make. However, the case is a good example of the concomitant spinal lesion that may exist, or preexist, when spinal anesthesia is given. The fact that a neurological syndrome appears shortly after the administration of spinal anesthesia does not permit omitting a thorough investigation for other possible etiologies.

### COMMENT

In all of the first four cases whose postanesthetic toxic neural complications were definitely established, the cocaine derivative used was known, one received pontocaine, two procaine and one metycaine. The sites of injection were the lumbar subarachnoid spaces between the third and fourth lumbar vertebrae or lower. In this series there was an instance of transverse myelitis, two cases of cauda equina neuritis and conus medullaris involvement and a case of pure pyramidal tract involvement. The time elapsing between the spinal anesthesia and the appearance of the neural complications was almost immediate in all cases. In one of the four cases the neurologic disturbances appeared within two to five days after the anesthetic.

Clinically all of these cases of post-spinal anesthetic neural complication showed little recovery after periods ranging from one to four years. The spinal fluid showed no characteristic picture. There was no pleocytosis or increase in spinal fluid total protein except in the third case.

One of our reported cases emphasizes the fact that occasionally spinal anesthesia may be falsely accused of causing neurological disturbances. This fact is further illustrated by the case reported by Pemberton<sup>16</sup>. Two of the cases in our series are presented to indicate the type of psychiatric complication one may encounter after spinal anesthesia in individuals predisposed to develop conversion hysteria immediately or remotely after their anesthesia experience.

*Clinical Sequelae* Stimulated by these experiences, we investigated the literature to determine the various reported neurological sequelae of spinal anesthesia. Hyslop has grouped the nervous sequelae according to whether they are of a focal or a general character, the former being subdivided into the remote and the adjacent types. For the purposes of this report it might be best to discuss the neurological syndromes in their approximate order of frequency.



*Headache* Headache is one of the most frequent complications of either spinal anesthesia or lumbar puncture. With Critchley we feel that this symptom occurs so often as scarcely to warrant its inclusion among the true neurological complications. Light and his coworkers,<sup>15</sup> from a survey of many articles, report the incidence of headache ranges from 0.1 to 83 per cent. The majority fall within the range of 1 to 25 per cent, comparable to that following lumbar puncture. It appears that headaches after spinal anesthesia seem to differ from the post-puncture headache in their greater frequency, in a greater liability to a severe and protracted course, and in the occasional development of complicating features, such as meningism or cranial nerve palsies.

*Cranial Nerve Involvement* Paralysis of the abducens nerve constitutes, according to the literature, the commonest nervous complication. In 1906, Becker<sup>17</sup> and Landow<sup>18</sup> reported such cases. In 1910 Reber,<sup>19</sup> in addition to his own cases, reviewed the literature and found 36 cases at that time. Blatt<sup>20</sup> in 1928 had collected 78 cases of abducens palsy following spinal anesthesia, and during the same year, at the Surgical Congress in Paris, 10 additional cases were reported, making a total at that time of 97 cases in all. Since 1928, approximately 30 cases have been reported. In 1937 Critchley reported two such cases. Hayman and Wood<sup>21</sup> reported two cases in 1942. Critchley's cases are typical of those reported in that the paralysis developed some days after the anesthetic, in association with severe headache. In both cases the ocular paresis was bilateral, although unilateral cases have more often been reported. Anderson stated that abducens paralysis may occur in from a few minutes to two weeks after the time of the injection of the anesthetic agent. It may be accompanied by photophobia as in some of the cases of Fawcett.<sup>22</sup> Chiene's<sup>23</sup> 30 cases varied in onset from the ninth to the twelfth postoperative day and the duration was from three weeks to six months. Ashworth's<sup>24</sup> patient completely recovered in eight weeks. In the cases of Rollet and Berard<sup>25</sup> the paralysis lasted for from one week to four months. In Hayman and Wood's two cases the palsy cleared in about three weeks. Hence, one can conclude that this lesion is usually transient and clears up in the course of a few days to months.

Other cranial nerve palsies have been occasionally reported. Jacqueau<sup>26</sup> has recorded optic atrophy and White-Morquecho<sup>3</sup> described transitory amaurosis in a case. Other authors have recorded lesions of the trigeminal, facial, auditory, and hypoglossal nerves. Paralysis of the seventh, eighth, and ninth cranial nerves has been observed by Angelescu and Tzovaru.<sup>27</sup>

*Cauda Equina and Conus Medullaris Lesions* This type of sequel has been recorded frequently in the literature. Both Critchley and Ferguson point out that the syndrome is one which might easily be overlooked, especially when represented chiefly by urinary retention and sacral analgesia. Thus, White-Morquecho reported 19 cases of slight bladder paresis and anal incontinence in six patients, in a series of over 3,000 cases of spinal anesthesia. Egonova in a collection of 180 cases found sphincter disturbances

in 13.8 per cent and a diminution or loss of the deep tendon reflexes of the lower extremities in 15.6 per cent. Critchley reported eight cases and Ferguson and Watkins recorded 14 cases characterized by bowel and bladder sphincter disturbance, and signs such as sacral sensory loss and alteration in the tendon reflexes of the lower extremities. More recently, Pearson and Twomey<sup>4</sup> have recorded a case and reviewed the literature. They point out that in these cases the most striking and most serious symptom was immediate retention of urine, followed at a later period by incontinence. The patients continued to have residual urine and difficulty in urination for periods varying from several weeks to more than two years. The less serious symptoms in this group (although it was the most serious in our patient, C. B.) consisted of loss of anal tone, an area of saddle anesthesia and diminution or absence of the deep tendon reflexes of the legs. In some cases cystometric and cystoscopic studies were made after a period of several months and the patients were found to have trabeculated, hypertonic bladders, associated with a variable amount of residual urine. Ferguson and Watkins found that complete urinary retention developed after operation in all their 14 cases except one whose bladder disturbance was incontinence on one occasion. The period of complete retention varied from about one week to a month, and was followed by incontinence. The latter was usually of short duration (a few weeks), but in two cases was still present after more than two years. Incontinence of feces lasted less than one month in six cases. In three patients it lasted about three months, and in one about six months. A sense of numbness in the saddle area was still present in some of the patients three years after operation. In three of Critchley's eight cases the symptoms of this syndrome showed some clinical evidence of improvement in three weeks, in four others, however, symptoms persisted without change up to the time of death. Brock, Bell and Davison's fifth case regained the ability to take a few steps five months after the onset, but the sphincters and sensory and reflex status remained unchanged. This evidence of permanent damage is present in the two cases reported by us. Kamman and Baker<sup>7</sup> reported similar experiences in three cases, as have Silva<sup>28</sup> and Boisseau<sup>29</sup>.

*Neuritis and Radiculitis* Loeser<sup>12</sup> has reported five cases of peripheral neuritis affecting isolated peripheral nerves which he had seen in one year. He is of the opinion that this is a more frequent complication than the literature would indicate. In his series of cases, three had involvement of the ulnar nerve, one of the sciatic and one presented paresthesias and sensory changes of both lateral cutaneous nerves of the thigh. He felt the original process was an arachnoiditis, the inflammatory process extending to the cord and ultimately involving the peripheral nerves from one to three weeks after the administration of anesthesia. Brock, Bell and Davison in their series include a case of lumbar radiculitis which appeared three weeks after the spinal anesthesia. Jones<sup>30</sup> has reported a case of sciatic pain lasting six months. Critchley described a case of sacral radiculitis which came on 24

days after the anesthesia Lindemulder<sup>8</sup> regards pains in the extremities as constituting the commonest sequel. In three of his cases pain in the legs persisted for several months and was associated with marked tenderness of the muscles. As a rule, in most of these reported cases, the symptoms improved gradually and full recovery occurred. Many writers, such as Blatt, Dassen,<sup>31</sup> Anderson<sup>32</sup> and Critchley, report the presence of lancinating pains, anesthetics and trophic changes. However, in these cases there was usually evidence of a more widespread morbid process affecting the roots and cord, in the nature of a myeloradiculitis. Anesthetic areas of the body may be the site of complicating trophic disorders including, of course, severe bed sores. Hyslop has described two cases in which a herpetiform eruption appeared over the lumbar dermatomes after spinal anesthesia.

*Myelitis, Meningomyelitis and Myeloradiculitis* In a smaller group of reported sequelae there is evidence of a more widespread morbid process affecting the cord, and, on occasions, the meninges and roots at a higher level. Cases of transverse, diffuse or ascending myelitis have been reported following spinal anesthesia. Smith<sup>33</sup> observed a complete transverse myelitis in the ninth thoracic segment which appeared on the seventeenth post-operative day. Franke<sup>34</sup> described two such cases with permanent paralysis. Degenerative myelitis has been reported by Nonne and Demme.<sup>35</sup> Devraigne and his co-authors<sup>36</sup> had a case of quadriplegia of transient duration following anesthesia. MacLachlan<sup>37</sup> has recorded a case of disseminated encephalomyelitis and Donovan and his colleagues<sup>38</sup> have described a case of meningomyelitis following spinal anesthesia. In the fifth case reported by Brock et al a toxic myelopathy occurred. Necropsy revealed apparent softening of the cord at the twelfth thoracic and first lumbar levels. Over a wider longitudinal extent there were found changes in the myelin sheaths, axis cylinders and glia, most marked at the periphery and also at the root-entry zones. Hewer<sup>39</sup> described a patient who developed a myelitic syndrome after pericaine anesthesia. Nine months later a laminectomy was performed revealing a constricting band of adhesive arachnoiditis around the lower part of the spinal cord and the upper portion of the cauda equina. Improvement occurred after operation. Kamman and Baker have recently reported a case of flaccid paraplegia immediately following spinal anesthesia which resembled a similar case recorded by Koster and Weintrob.<sup>40</sup> The necropsy on the patient of Kamman and Baker disclosed an adhesive leptomeningitis of the middle and lower thoracic spinal cord. In some areas this membrane had become hyalinized. In this area of the cord the posterior columns were replaced by a large area of softening. The remaining white and gray matter was severely damaged. Demyelination was prevalent in the posterior and lateral columns of the lower thoracic, lumbar and sacral segments of the spinal cord. Hammes recorded two cases which manifested themselves with a syndrome of a slowly ascending myelitis. Both developed evidences of spinal fluid block. One of the cases was explored and a dense pachyleptomeningitis was found for the entire distance of the cord exposed.

at laminectomy Hammes concluded that inflammatory and fibrotic changes had developed in the meninges due to the anesthetic. An extension of this process with subsequent involvement of the spinal cord circulation explained, he thought, the clinical syndrome of a slowly ascending myelitis. Brain and Russel<sup>41</sup> reported a somewhat similar case following spinocaine anesthesia. The spinal fluid was normal eight weeks postoperatively. The patient died 16 weeks later and pathologic examination revealed a massive softening of the spinal cord up to the twelfth thoracic segment, with inflammatory reaction in the pia, and perivascular changes. Another example of this type of complication is offered by the sixth case in the series reported by Brock et al. This patient developed a cauda equina neuritis following spinal anesthesia. During the next 29 months a transverse myelitis and radiculitis developed, which ultimately proved fatal. The clinical course was characterized by long periods during which the condition was stationary. With subsequent exacerbations higher levels of the cord become involved. They suggest that the original chemotoxic effect on the spinal cord by the anesthetic may have devitalized the neural tissue so that other factors, such as a dormant virus, may have become active and caused further involvement.

*Focal Cerebral Lesions* It is difficult to say in any case in which hemiplegia occurs after spinal anesthesia that it was definitely due to the anesthetic agent. Cutchley described a patient who developed mental symptoms and a transient hemiplegia immediately following spinal anesthesia. He suggested the possibility of cerebral angiospasm or a small thrombosis, due in part to an associated vascular disease. Behrend and Riggs<sup>42</sup> and Watter<sup>43</sup> reported similar cases. The first authors felt the sequel was due to a relative cerebral anoxia produced by an alteration in blood pressure occurring as a result of the effect of the surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency. Watter stressed the factor of stagnant anoxia caused by spinal anesthesia as the precipitating factor. Other cases of hemiplegia following spinal anesthesia have been recorded by Arnheim and Mage,<sup>44</sup> Schreiber,<sup>45</sup> Bona<sup>46</sup> and Yamanuti.<sup>47</sup>

*Meningitis* The occurrence of meningitis following spinal anesthesia is perhaps the most easily explained of all the complications and can be prevented by aseptic technique.

Aseptic meningitis following spinal anesthesia has been recorded by Brock, Bell and Davison in the same way as it has been reported very occasionally as a complication of simple lumbar puncture (Reynolds and Wilson<sup>48</sup>).

*Neurological Disease Precipitated by Spinal Anesthesia* Preëxisting disease of the central nervous system is given as a contraindication to spinal anesthesia by some authors. It is a well recognized fact that the first clinical manifestations of some clearly defined nervous disorder may date from a severe trauma, operation or confinement. It is an accepted fact that cerebral trauma may precipitate, aggravate or accelerate the degenerative process of general paresis or cerebral arteriosclerosis. Spinal anesthesia may also be

a precipitating agent in the evolution of certain neurological affections Hammes,<sup>9</sup> based on his experience, concludes that the depressing effect on the circulation of the anesthesia and the hemolytic and myelitic action of the toxic drug may hasten an underlying degenerative process and increase the clinical symptoms Gritchley cites a case of multiple sclerosis and another of progressive muscular atrophy the first signs and symptoms of which came on almost immediately after spinal anesthesia Synder and Synder<sup>40</sup> record a case of meningovascular syphilis which flourished clinically immediately following the anesthetic experience Other instances of acute onset of central nervous system syphilis after spinal anesthesia are reported by Faure-Beauhieu,<sup>50</sup> La Cava,<sup>51</sup> and Donovan and colleagues<sup>78</sup> Hammes also reports two cases of neurosyphilis (tabes dorsalis and paresis) which were precipitated by spinal anesthesia This author admits that he has observed several patients with tabes and one with cerebrovascular syphilis who did not show any increase in the neurological syndrome following spinal anesthesia for abdominal surgery In his paper Hammes also records a case of multiple sclerosis and one of posterolateral sclerosis, secondary to pernicious anemia, where the clinical progress was unusually rapid and marked following spinal anesthesia Although no definite conclusions can be drawn as to the causative relationship, these cases demonstrate that the chemotoxic effect of the various spinal anesthetics may precipitate symptoms and aggravate preexisting neurological disease

*Pathogenesis of the Neurological Sequelae* Numerous observers and experimenters have reported the postmortem changes in the central nervous system following spinal anesthesia Pathologic changes have been reported by Nonne and Demme, Spielmeyer, Lindemulder, MacLachlan, Brock, Bell and Davison, Brain and Russel, and others The lesions observed are usually degenerative changes in the cord, demyelination and atrophy with evidence of glial reaction, together with a varying degree of meningeal reaction Myelomalacia was found in the cases reported by Brain and Russel and by Kamman and Baker Chronic adhesive arachnoiditis and pachymeningitis have been present at necropsy associated with the above findings of toxic myelitis

From the experimental work done there is positive evidence that various cocaine derivatives have a toxic destructive effect on nerve tissue when injected intrathecally Wossidlo<sup>72</sup> found changes in the nerve cells up to 24 hours after subarachnoid injection of procaine in rabbits and dogs Transitory changes in nerve cells had also been reported by Van Lier<sup>65</sup> Davis and his associates,<sup>74</sup> after injecting a series of common anesthetic substances intrathecally in dogs, found various changes which made them conclude that these drugs had a hemolytic and myelolytic action on the spinal cord They reported the following changes

1. A varying degree of meningeal inflammation as a constant finding
2. Changes in the ganglion cells

3 Swelling and fragmentation of the axis cylinders with degenerative changes in the fiber tracts It was noted that the degenerative and cellular changes were inconstant in animals allowed to live 90 days or more but that the meningeal reactions were constant and marked Spielmeyer<sup>55</sup> had previously reported essentially similar observations in his experimental animals and had concluded that there was a direct toxic action on the axon cylinders with subsequent secondary retrograde degeneration of the ganglion cells In line with his conclusions are the pathological findings reported by Brock and co-workers in a case of acute myelitis following spinal anesthesia There was extensive destruction of the myelin sheaths, axis cylinders and glia, mostly at the periphery of the cord and at the zones of entrance of the posterior roots The ganglion cells of the anterior and lateral horns were also slightly involved Lundy and his co-workers<sup>56</sup> studied the changes in the spinal cord produced by a dose of procaine sufficient to cause permanent and fatal paralysis They found peripheral degeneration of the myelin in the anterior, lateral and posterior columns of the spinal cord Haven<sup>57</sup> in his experiments found an inflammatory reaction of the meninges similar to that which had been reported by Davis and his co-workers, which in the older animals reached a stage of fibrotic scarring McDonald and Watkins<sup>58</sup> reported that intrathecal injections of spinal anesthetic solutions in cats in concentrations commonly employed clinically, though in relatively larger doses, could produce lasting paralysis comparable to lesions of the cauda equina On the other hand, Koster and Kasman<sup>59</sup> were unable to demonstrate any pathologic changes in the spinal cord of autumn frogs or in human cords after spinal anesthesia

In spite of the accumulated reports of postmortem material and experimental work, the question of etiology in many of the neurological sequelae of spinal anesthesia remains unsettled In most of the cases the neural syndromes so speedily followed the intrathecal injection of the spinal anesthesia as to suggest a direct chemotoxic effect of the cocaine derivatives on the neuroaxis It must be emphasized, however, that the direct chemotoxic effect does not entirely explain the causation of many of the neural complications There is the fact that the great majority of patients operated upon under spinal anesthesia do not develop neurological sequelae Furthermore, the cases reported in which the interval between the anesthesia and the onset of symptoms is relatively long, suggest the possible intervention of other factors This consideration is also pertinent in the reported cases of remote complications of spinal anesthesia such as isolated cranial nerve involvement or focal cerebral damage The suggestion is presented by some writers that some of the nervous sequelae are due merely to the activation of a latent morbid process within the nervous system or by activated latent organisms of low toxicity which produce a low grade meningitis This type of pathologic process might explain the cases in which the neurologic syndrome is progressive after spinal anesthesia Here one must assume that the original chemotoxic effect permitted other factors (virus?) to operate

on neural tissue devitalized by the anesthetic Behrend and Riggs emphasize that the anoxia caused by the circulatory depression following the anesthetic may be the underlying factor in the production of cerebral neurological sequelae especially in the presence of impaired cardiocirculatory efficiency Watter also believes that the stagnant anoxia caused by spinal anesthesia, in the presence of chronic anemia, heavy premedication or other factors which help further to impede the utilization of oxygen, can produce cerebral complications Brock and his colleagues feel there may be a tissue sensitivity to the cocaine derivatives in certain individuals which predisposes them to the development of neurological complications There is, of course, no way of determining whether or not a patient's nervous tissues are oversensitive to the cocaine anesthetics

### SUMMARY AND CONCLUSIONS

Six cases of neuropsychiatric complications associated with spinal anesthesia are reported Four of these cases occurred immediately following the use of the anesthetic agent and present syndromes of serious myelitic or myeloradicular nature Little or no recovery occurred in all Two of the reported cases were in the nature of conversion hysteria "paralysis" of the lower extremities The conversion mechanism was conditioned by the patient's subjective experience with spinal anesthesia A case of metastatic spinal cord neoplasm, which came to light immediately following spinal anesthesia, is presented to illustrate the importance of keeping in mind the possibility of preëxisting neurologic disease when evaluating the rôle of spinal anesthesia in the causation of postoperative neurologic sequelae

From this study it is obvious that neurological complications of great diversity, either immediate or remote, mild or severe, temporary or permanent, may follow spinal anesthesia Undoubtedly many complications are not recognized and some are not reported in the literature

Serious complications in normal individuals are relatively infrequent and in properly selected cases spinal anesthesia holds an important and almost indispensable place in the surgeon's armamentarium

### BIBLIOGRAPHY

- 1 EVERTT, J M • Fourteen hundred and fifteen spinal anesthetics with special reference to indications, complications and mortality, *Virginia Med Monthly*, 1935, *lxii*, 304-309
- 2 FOSS, H L, and SCHWALM, J L • Relative merits of spinal and ether anesthesia, *Jr Am Med Assoc*, 1933, *ccccc*, 1711
- 3 WHITE-MORQUECHO, J • Accidents and emergencies of spinal anesthesia, *Anesth and Analg*, 1939, *xviii*, 82-85
- 4 PIERSON, E L, and TWOTY, C F • Neurogenic dysfunction of the bladder due to spinal anesthesia, *New England Jr Med*, 1940, *ccxxiii*, 171-174
- 5 FERGUSON, F R, and WATKINS, K H • Paralysis of the bladder and associated neurological sequelae of spinal anesthesia (cruda equina syndrome), *Brit Jr. Surg*, 1937-1938, *xxv*, 735-751
- 6 HAMMES, E M • Neurological complications associated with spinal anesthesia, *Minnesota Med*, 1943, *xxvi*, 339-345

- 7 KAMMAN, G R, and BAKER, A B Damage to the spinal cord and meninges following spinal anesthesia, *Minnesota Med*, 1943, xxvi, 786-791
- 8 LINDEMULDER, F G Spinal anesthesia, *Jr Am Med Assoc*, 1932, xcix, 210
- 9 HYSLOP, G H Spinal anesthesia Nervous system sequelae, *Surg, Gynec, and Obst*, 1933, lvi, 799
- 10 BROCK, S, BELL, A, and DAVISON, C Nervous complications following spinal anesthesia, *Jr Am Med Assoc*, 1936, cvi, 441-446
- 11 JARMAN, R Recent advances in anaesthetics, *Brit Med Jr*, 1934, i, 796-799
- 12 LOESER, L H Peripheral neuritis as a sequela of spinal anesthesia, *Jr Am Med Assoc*, 1933, ci, 31-32
- 13 EGOROVA, M A Complications of spinal anesthesia, *Khirurgiya*, 1939, vi, 37
- 14 CRITCHLEY, M Neurological sequelae of spinal anaesthesia, *Proc Roy Soc Med*, 1937, xxx, 63-68
- 15 LIGHT, G, SWLET, W H, LIVINGSTON, H L, and ENGEL, R Neurological changes following spinal anesthesia, *Surgery*, 1940, vii, 138-153
- 16 PEMBERTON, J DEJ Discussion of another paper, *Proc Staff Meet Mayo Clin*, 1933, viii, 308
- 17 BECKER E Operationen mit Rückenmarksanästhesie, *München med Wchnschr*, 1906, liii, 1344
- 18 LANDOW, M Ein Fall von doppelseitiger Abduzenslahmung mit Nackenschmerzen nach Rückenmarksanästhesie, *München med Wchnschr*, 1906, liii, 1464
- 19 REBER, W Ocular palsies associated with induction of spinal anesthesia by various solutions, *Sec on Ophth Am Med Assoc*, 1910, 255
- 20 BLATT, N Neuropathie und neuropathische Konstitution als predisponierende Faktoren für Augenmuskellähmungen nach Lumbalanästhesie, *Wien med Wchnschr*, 1929, lxxix, 1391-1396
- 21 HAYMAN, I R, and WOOD, P M Abducens nerve paralysis following spinal anesthesia, *Ann Surg*, 1942, cxv, 864-868
- 22 FAWCETT, K R Extraocular muscle paralysis following spinal anesthesia, *Minnesota Med*, 1931, xiv, 648
- 23 CHIENE, G Discussion on spinal anaesthesia, *Brit Med Jr*, 1909, ii, 785
- 24 ASHWORTH, H K Nervous sequelae of spinal anaesthesia, *Proc. Roy Soc Med*, 1933, xxvi, 501
- 25 ROLLET, J, and BERARD, P Les paralysies oculaires consecutives a la rachianesthésie, *Jr de med de Lyon*, 1928, cxvii, 167
- 26 JACQUAU, N Atrophie optique double consecutive a la rachianesthésie, *Lyon med*, 1927, cxviii, 547
- 27 ANGELESCU, C, and TZOVARU, S Reflexions sur quelques faits concernant les paralysies des nerfs moteurs cramo-rachidiens post-rachianesthésiques, *Presse med*, 1931, xxxix, 1855-1857
- 28 SILVA, C By-effects of intraspinal anesthesia, *Arch de Med de Pernambuco*, 1925, i, 47
- 29 BOISSEAL, J Lésion persistante des 3 es, 4 es, 5 es et 6 es racines sacrees consecutives a une rachianesthésie, *Rev neurol*, 1930, i, 1148
- 30 JONES, H W One thousand spinal anesthetics with special reference to complications and mortality, *Ann Surg*, 1932, xcvi, 85
- 31 DASSEN, R Syndrome piramidale consecutive a una raquianestesia, *Semana med*, 1935, i, 1145
- 32 ANDERSON, E R Complications of spinal anesthesia, *Jr Lancet*, 1931, li, 403
- 33 SMITH, W A Neurologic hazards of spinal anesthesia, *Jr Med Assoc. Georgia*, 1933, xxi, 297
- 34 FRANK, M Über Dauerschädigungen nach Lumbalanästhesie mit Novocain-Suparenin Lösung, *Deutsch Ztschr f Chir*, 1927, cxi, 262



- 35 NONNE, M, and DEMME, H Degenerative Myelitis nach Spinalanästhesie, *Wien klin Wchnschr*, 1928, xli, 1002
- 36 DEVRAIGNE, SUZOR, and LAENNEC A propos de l'anesthésie rachidienne, observation de quadriplégie après rachianesthésie guérie rapidement, *Bull Soc d'obst et de gynéc*, 1927, xvi, 319
- 37 MACLACHLAN, T K Disseminated encephalomyelitis following spinal anaesthesia, *Brit Med Jr*, 1931, ii, 11
- 38 DONOVAN, R, BERTERVIDE, J J, and RECHNIEWSKI, C Meningo-mielitis enum heredo-especifici consecutiva a una raquianesthesia, *Rec Soc de méd int y tisiol*, 1928, iv, 67
- 39 HEWER, C L Discussion of Ashworth's <sup>24</sup> paper, *Proc Roy Soc Med*, 1933, xxvi, 507
- 40 KOSTER, H, and WEINTROB, M Complications of spinal anesthesia, *Am Jr Surg*, 1930, viii, 1165-1179
- 41 BRAIN, R, and RUSSEL, D Myelomalacia following spinal anaesthesia, *Proc Roy Soc Med*, 1937, xxx, 1024
- 42 BEHRFND, A, and RIGGS, H E Cerebral complications following surgical operations, *Arch Surg*, 1940, xl, 24
- 43 WATTER, L Hemiplegia following spinal anesthesia, *Am Jr Surg*, 1941, liii, 359
- 44 ARNHEIM, E E, and MAGE, S Spinal anesthesia, analysis of 497 cases, *Ann Surg*, 1931, xciii, 929
- 45 SCHREIBER, F Cerebral anoxia and anaesthesia, *Trans Am Soc Anesth*, 1939, v, 5
- 46 BONA, T Beitrag zum Studium der Hirnkomplikationen nach Bauchoperationen und Lumbalanästhesien, *Zentralbl f Chir*, 1938, lxxv, 1985
- 47 YAMANUTI, H Erfahrungen mit Oberbauchoperationen unter Spinalanästhesie ein Fall von Lahmung der rechten oberen Extremität und Aphasie nach Spinalanästhesie, *Zentralbl f Chir*, 1938, lxxv, 2714
- 48 REYNOLDS, K E, and WILSON, G Three cases of aseptic meningitis following lumbar puncture, *Jr Am Med Assoc*, 1934, ci, 1460
- 49 SYNDER, W H, and SYNDER, M H Acute onset of central nervous system syphilis after a spinal anaesthesia, *Anaesth and Analg*, 1939, xviii, 224
- 50 FAURE-BEAUMIEU, M Results of spinal anesthesia in patient with neurosyphilis, *Presse med*, 1933, xli, 2045
- 51 LA CAVA, G Spinal anaesthesia and progressive paralysis, *Policlinico (sez prat)*, 1934, xii, 1206-1211
- 52 WOSSIDLO, E Experimentelle Untersuchungen über Veränderungen der Nissl'schen Granuli bei der Lumbalanästhesie, *Arch f klin Chir*, 1908, lxxvii, 1017-1053
- 53 VAN LIER, E H Histologischer Beitrag zur Rückenmarksanästhesie, *Beitr z klin Chir*, 1907, lv, 413
- 54 DAVIS, L, HAVEN, H, GIVEN, J H, and EMMET, J Effects of spinal anesthetics on the spinal cord and its membranes, *Jr Am Med Assoc*, 1931, xcvi, 1781
- 55 SPIHMEYER, W Veränderungen des Nervensystems nach Stovain-Anästhesie, *München med Wchnschr*, 1908, lv, 1629-1634
- 56 LUNDY, J S, ESSEN, H E and KERNOHAN, J W Experiments with anesthetics, *Jr Am Med Assoc*, 1933, ci, 1546
- 57 HAVEN, H Discussion, *Jr Am Med Assoc*, 1933, ci, 1551
- 58 McDONALD, A D, and WATKINS, K H An experimental investigation into the cause of paralysis following spinal anesthesia, *Brit Jr Surg*, 1938, xxv, 897
- 59 KOSTER, H, and KASMAN, L P Histologic studies of the spinal cord following spinal anesthesia, *Am Jr Surg*, 1934, xxx, 277

# ATROPHIC ARTHRITIS ASSOCIATED WITH SPLENOMEGALY AND LEUKOPENIA \*

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IN 1924 Felty<sup>1</sup> reported the cases of five adults who had atrophic arthritis associated with splenomegaly and leukopenia. The age of the patients ranged from 45 to 65 years. Their arthritis was generalized, relatively benign, and of at least two years' duration. All patients had suffered recent, marked weight loss. Each had a palpably enlarged spleen that was firm and non-tender. Three of the five had enlarged axillary, inguinal or epitrochlear lymph nodes, and all had some degree of yellow-brown pigmentation of the skin, chiefly on the exposed surfaces. Four of the patients had a slight microcytic anemia, and their leukocyte counts varied between 1,000 and 4,200. Felty considered that there were two possible explanations for this unusual combination of findings in persons suffering from a very common basic disease: (1) "The several features are manifestations of one pathologic process, caused by a noxa which simultaneously affects the joints, the spleen, and the blood leukocytes (and in three of the five cases the lymph glands)", (2) "The syndrome is merely the confusion of two separate clinical entities, occurring coincidentally in the same individual." If the second explanation were correct, it would be necessary to assume the arthritis to be independent of the rest of the complex, and Felty thought this to be unlikely "on the law of probability alone." Therefore, he stated "one is more or less forced to the conclusion that this syndrome is a distinct clinical entity, of which the outstanding symptoms are those related to the joints, and the outstanding signs are the enlarged spleen and the blood picture."

Since the appearance of Felty's paper 23 cases have been reported under the name of "Felty's syndrome." It is certain that a far greater number has been observed. Throughout these records the validity of this syndrome as a distinct clinical entity is challenged, either through expressed or implied uncertainty. Unfortunately much of the material presented, and this includes all of Felty's original cases, has been studied without benefit of biopsy or autopsy examination. The value of these discussions is correspondingly lessened. In other instances, one of which must be included in the cases to be presented in this report, thorough tissue study has failed to provide a clear explanation of the morbid forces responsible for the clinical observations.

Three patients with the essential features of Felty's cases were seen at Laguna Honda Home in the past year. It is the purpose of this paper to present the clinical and autopsy studies of this group and briefly to review only those earlier discussions that contained pathologist's reports, thus, con-

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clusions may be made that might aid somewhat toward an ultimate sound evaluation of the several features which compose this syndrome

### CASE REPORTS

*Case 1* The clinical course of J C, white male laborer and watchman, was followed continuously at the out-patient clinics of the University of California Hospital and at Laguna Honda Home from June 29, 1933 when, at the age of 53, he was first seen at the Clinics with a complaint of stiff ankles of two and one half years' duration. His family history was without significance. His past and systemic histories revealed that he had had no serious childhood diseases, tonsillectomy at an early age, "rheumatism" in his feet when 29, acute gonorrhea at 20, and again at 49. In the past he had been a "heavy drinker." He still smoked heavily but used no drugs.

In 1931, at the age of 51, he first noted pain and swelling of his left ankle. This was two and a half years after his last attack of acute gonorrhea. During the following two years his shoulders, elbows, ankles, and fingers were affected at times by pain, swelling, redness. Despite an adequate diet he lost 22 pounds between March and June of 1933. During the preceding two years he had received physiotherapy and injections of an unknown material.

His physical examination in June, 1933, showed a rather pale skin without abnormal pigmentation. He was edentulous, his tonsils were absent, and his heart, lungs, abdomen, and spine were normal. He had no enlarged lymph nodes. His forearm and shoulder muscles were moderately wasted. The ankle joints were swollen and showed bony enlargements. All joints of the extremities were stiff, the knees were limited to 90 per cent of normal motion, and the shoulders to 70 per cent. The elbows were partially ankylosed. The fingers showed early deformity. Roentgenographic studies were reported as "atrophic arthritis of the elbows," and a "combination of atrophic arthritis and flat foot." Genito-urinary examination failed to find any evidence of active gonorrhea. His urine was negative, hemoglobin 94 per cent, red cells 4,650,000, white cells 12,320 with normal distribution of cell types, blood Wassermann and Kahn reactions negative.

In November, 1933, he was seen in the skin clinic where a diagnosis of psoriasis was made and Fowler's solution prescribed. His arthritis was treated with six injections of typhoid vaccine in July, 1933, from this time until 1942 he was given repeated series of body bakes and physiotherapy and frequent intravenous injections of ascorbic acid. His course showed periodic improvement and relapse. In November, 1937, his spleen was first palpable, and his leukocyte count, which had previously been between 7,760 and 12,320 was then 1,600 to 3,500. At this time his blood uric acid level was 3.1 mg per cent, urine negative, phenolsulfonphthalein clearance 62 per cent. Large lymph nodes were felt in the axillae and smaller ones in the inguinal regions. From 1937 until September 1943, he continued to be ambulatory and suffered occasional exacerbations of both his arthritis and psoriasis. During this period a rose bengal test indicated normal liver function, a complete gastrointestinal roentgen-ray series was negative, marrow obtained by sternal puncture showed moderate myeloid hyperplasia, blood platelets were repeatedly reported as normal, though no total counts are recorded, a mild hypochromic anemia and a definite leukopenia persisted.

On September 1, 1943, he "wrenched his right knee." During the next week this became painful, swollen, and intensely inflamed. He was admitted to the Laguna Honda infirmary on September 7 with a fever of 103.6° F. Examination of the head, neck, and thorax was without significant finding. The spleen was firm, non-tender, and extended 10 to 12 centimeters below the left costal margin. Small, indolent lymph nodes were felt in both axillae and in the inguinal regions. The hands were affected

especially by chronic arthritic enlargement of the metacarpo-phalangeal joints, though there was some stiffness of the interphalangeal joints as well, fusiform deformity of the fingers was not prominent. The wrists, elbows, shoulders, ankles, toes, and left knee were stiff in varying degrees, but none of these joints was tender. The hips seemed unaffected. The right knee joint was swollen, red, painful, and hot, there was some extension of the inflammation above the knee both anteriorly and posteriorly. In the next few days the right popliteal area became more indurated, red and tender, and a milder inflammation spread half way up the posterior thigh. Though the leukocyte count was only 2,320, sulfadiazine was prescribed against this apparent cellulitis. The superficial signs of infection subsided moderately during the following week, but induration and tenderness persisted in the popliteal space. The leukocyte count on September 15 was 5,000 with 75 per cent polymorphonuclear cells. On September 18 the patient developed a maculopapular rash, and the sulfonamide therapy was discontinued. On October 3 the popliteal space was clearly fluctuant. The abscess was incised, and 700 cubic centimeters of pus were removed which contained streptococci of unclassified type. Roentgenograms of the knee and femur revealed a chronic arthritis of the joint and no evidence of osteomyelitis of the bone. On October 13 an incision was made from the posterior mid-thigh to the popliteal space, opening all loculated collections of pus. The wound continued to drain, and granulation tissue formed slowly. Streptococci were regularly recovered from the smears. Blood cultures taken September 25, September 27 and October 28 were negative. A Congo red test performed on October 21 showed 63 per cent of the dye remaining in the plasma after one hour. Because of a slightly bloody diarrhea during the first week of November, stool examinations were made, these were negative.

During November and December the patient's course was quiet, the wound was slowly healing, and the drainage was slight. On January 5, 1944 his temperature rose suddenly to 104° F, and he became comatose. He was moderately cyanotic, his neck was stiff, the lower left thorax was dull to percussion, and moist râles were heard there. The abdomen was negative except for the large spleen. All reflexes were hypoactive or absent, and no abnormal reflexes were elicited. The leukocyte count was 2,000. Spinal fluid was under normal pressure, clear, without cells or elevated protein. The patient remained in coma, and the following morning both lungs were full of wet râles. He died later in this day.

The record of his blood studies is given in table 1.

*Autopsy* None of the joints was subjected to postmortem study. The heart was of normal size. The coronary vessels were widely patent, and the valves were but slightly sclerotic. There was some patchy fibrosis throughout the myocardium but no evidence of inflammation. The lungs had many adhesions on their surfaces. The bronchi were inflamed and contained purulent material. There was patchy bronchopneumonia in each lung, and in some areas this had progressed to frank abscess formation. The liver weighed 2,600 grams, had a slightly rounded margin, and was pale with a finely mottled appearance throughout. Microscopically the parenchyma was well formed with some slight fatty infiltration. There was no increased portal fibrosis, although in this area there was noted a diffuse leukocytic infiltration composed mostly of rather mature polymorphonuclear leukocytes and a few round cells. The portal blood vessels and bile ducts were normal. One portal vein contained an organized thrombus. The gall-bladder was large and contained stones. The pancreas, stomach, bowel, and bladder were without significant pathologic change. The spleen weighed 1,600 grams. The splenic veins were widely patent, and the arteries were normal. Microscopic examination showed the capsule and trabeculae to be relatively normal, and the pattern of the organ was preserved. The sinuses were not unusually dilated. Around the Malpighian bodies and the central arterioles there was an infiltration of a distinct, homogeneous, eosinophilic material which took the stain for amyloid and which occupied most of the areas of the Malpighian bodies.

TABLE I  
Blood Studies of Case 1

| Date     | Hgb*  | Rbc** | Wbc    | Pmn | Banded | Small L | Large L | Mono | Eos | Baso |
|----------|-------|-------|--------|-----|--------|---------|---------|------|-----|------|
| 8-28-33  | 13 67 | 4 65  | 12,320 | 70  |        | 20      |         | 10   |     |      |
| 11-24-33 | 14 50 | 4 95  | 7,760  | 67  |        | 18      |         | 9    | 6   |      |
| 3-13-34  | 14 25 | 4 70  | 7,950  | 61  |        | 38      |         |      |     | 1    |
| 6-11-35  | 11 60 | 4 56  | 11,400 | 49  | 16     | 17      |         | 18   |     |      |
| 11- 4-37 | 14 84 | 4 90  | 3,500  |     |        |         |         |      |     |      |
| 11-16-37 |       |       | 1,600  |     | 28     | 24      | 4       | 5    |     |      |
| 12-28-37 |       |       | 2,650  | 18  |        | 16      | 56      | 6    | 2   |      |
| 1-11-38  | 9 96  | 3 46  | 1,600  | 26  |        | 12      | 46      | 8    | 4   |      |
| 1- 7-34  | 12 70 | 4 41  | 2,520  | 55  | 7      | 32      |         | 3    | 3   |      |
| 1-30-42  | 11 80 | 4 19  | 2,200  |     |        |         |         |      |     |      |
| 6-15-43  | 12 00 | 4 44  | 3,280  | 58  | 34     | 40      | 1       | 1    |     |      |
| 6-19-43  | 12 69 | 4 63  | 4,160  | 25  |        | 15      | 37      | 22   | 1   |      |
| 7-27-43  | 14 12 | 4 96  | 1,840  | 32  |        | 19      | 42      | 4    | 2   | 1    |
| 9- 8-43  | 12 10 | 4 37  | 2,320  | 51  |        | 22      | 18      | 8    |     |      |
| 9-10-43  |       |       | 3,420  |     |        |         |         |      |     |      |
| 9-13-43  |       |       | 4,540  |     |        |         |         |      |     |      |
| 9-15-43  |       |       | 5,000  | 75  |        | 8       | 13      | 3    | 1   |      |
| 9-17-43  |       |       | 5,140  |     |        |         |         |      |     |      |
| 9-29-43  | 11 59 |       | 4,460  | 74  |        | 18      | 7       |      |     |      |
| 10- 1-43 |       |       | 5,520  | 74  | 12     | 13      | 8       | 3    | 2   |      |
| 10- 4-43 |       |       | 4,160  | 76  | 16     | 11      | 10      | 2    | 1   |      |
| 10- 7-43 |       |       | 3,160  | 54  |        | 17      | 21      | 6    | 1   | 1    |
| 10-11-43 |       |       | 4,720  | 49  |        | 16      | 32      | 2    | 1   |      |
| 10-25-43 | 10 40 |       | 5,160  |     |        |         |         |      |     |      |
| 1- 5-44  | 6 90  |       | 2,000  | 42  |        | 16      | 33      | 7    | 1   |      |

\* Hemoglobin in grams per 100 c c of blood

\*\* Red cells in millions per cubic millimeter

The surrounding stroma showed some fibrosis and scattered plasma cells and lymphocytes, there was no evidence of abnormal cellular infiltration. The adrenals were of normal size with clear cortico-medullary distinction. On section the pattern of these organs was found to be strikingly deformed by the presence of a diffuse infiltration of an amyloid-staining material that mainly occupied the cortex. Much of this material was extracellular and crowded out many areas of the cortical fascicular layers. The medullary tissue was not abnormal. The kidneys were normal on gross examination. Microscopically their capsules appeared smooth, and the glomeruli were for the most part well preserved and without evidence of crescent formation or adhesions. A few glomeruli, however, contained hyalinized tufts which stained as amyloid. The prostate was normal except for rare inflammatory cells. Sections of lymph nodes were taken from many parts of the body. All of these had a well preserved pattern with distinct lymphoid elements. In some areas the sinusoids were rather prominent and contained many cells apparently of the reticulo endothelial system. Bone marrow specimens were taken from rib, sternum, and vertebral bodies. All of the marrow tissue showed a diffuse replacement by large sheets of relatively uniform cells which were of moderate size with a moderately eosinophilic cytoplasm and usually with vesicular nuclei. These cells were very young, and the absence of more mature cells of their type made their identity uncertain. Occasional polymorphonuclear leukocytes were seen. Mature cells of the monocytic series were scant, and only rare lymphocytic cell type were noted. Erythrocytic hemopoiesis was nearly absent, scattered megakaryocytes were seen.

*Comment.* This case presents several problems. First, the arthritis was of debated type. During the last few years of life this process was quiescent,

and one is forced to consider it from the history and from the impressions of those clinicians who followed the patient's course during the time that the disease was most troublesome. The patient had had two apparently separate attacks of acute gonorrhea, the first when he was 20, the last when he was 49. The first definite arthritis appeared when he was 51, yet in his past history he mentioned "rheumatic pains in the feet" at the age of 29. Gonorrheal arthritis most commonly begins within a few weeks after the onset of the primary attack. However, it is well known that cases do occur many months, and even many years, after the primary infection. No evidence of active gonorrhea was present at the time the patient suffered his most acute joint inflammation. The history of "rheumatic pains" at the age of 29 followed, at 51, by an acute, polyarticular arthritis which affected mainly the smaller joints is quite compatible with a diagnosis of atrophic arthritis. On the bases of the clinical and roentgen-ray appearance of these joints and the course of the affection over a 10 year period orthopedic and medical consultants considered the arthritis definitely to be of the atrophic type.

The second problem is that of the splenomegaly. This is readily explained by the amyloidosis, which was sufficiently widespread throughout the organ to account for its enlargement. However, there remains the question of how best to explain the presence of this amyloid deposit. Several cases have been reported in which chronic atrophic arthritis was found at autopsy to be associated with extensive amyloidosis. These reports include five cases of children afflicted with Still's disease and at least three cases occurring among adults.<sup>2</sup> Other patients in the older age group are mentioned in various discussions concerned particularly with amyloid disease,<sup>3</sup> but in these the type of arthritis is not stated or is uncertain. None of these patients had a history of suppurative disorder, and none suffered from any other disease that is commonly related to amyloid deposit. In two of the adult patients prolonged courses of vaccine therapy were considered, on theoretic grounds, as the possible agent effecting the amyloid response.<sup>4</sup> The patient under present discussion received some injections of an unknown material during his first two years of illness. Subsequently he was given six injections of typhoid vaccine, this was followed by parenteral vitamin C at frequent intervals for a two or three year period. His spleen was not palpable until five years after his first injections and four years after his single course of typhoid therapy. Vitamin C is not an agent which is known to provoke amyloid deposit. It seems unlikely that any of these agents was responsible for the amyloidosis noted in the present case. The patient's final illness, which lasted four months, was dominated by a large suppurating wound that resulted from a streptococcic abscess. Though cases are mentioned in which amyloidosis has developed within periods as short as four months, this experience is decidedly uncommon. Furthermore, since it seems evident that the amyloidosis was the essential cause of the splenomegaly in this case,

it must have been present at least six years before the onset of his ultimate streptococcic infection

The liver was affected by an apparently chronic, subacute portal hepatitis, but there was no evidence of true portal cirrhosis. As congestion was not present in the spleen, the enlargement of this organ was presumably unrelated to the liver disease.

The leukopenia, moderate anemia, and the microscopic appearance of the bone marrow are not readily explained. Leukopenia occurs in otherwise uncomplicated chronic atrophic arthritis in percentages estimated from 0.5 to 22 depending upon the strictness with which the term is defined.<sup>5</sup> Anemia is more common. The large numbers of young cells in the marrow were of unidentifiable type, but the appearance of the marrow was not that of a leukemia. Maturation of all leukocytes seemed depressed, and evidence of erythrocytic hemopoiesis was scant. The factors responsible for these findings are unknown.

*Case 2* M. M., a 75 year old, white, German widow, entered Laguna Honda Home on March 13, 1943 because of incapacitating chronic atrophic arthritis of 20 years' duration. She was born in Germany, and came to the United States in 1913. Her family history was without significance. She used neither alcohol nor tobacco and had taken no drugs routinely other than aspirin.

In her past history there were no unusual childhood diseases. She had had pneumonia in 1920. In 1934 she entered the San Francisco Hospital because of jaundice that followed a year of frequently recurring attacks of severe right upper quadrant pain. There was radiation of the pain to the right shoulder and interscapular region. Her liver was felt two fingers' breadth below the right costal margin. The spleen was not palpable. A gastrointestinal series was negative, and the gall-bladder failed to visualize for roentgen-ray examination after the administration of oral dye. She had no anemia at this time, but the white cell count was 6,600 with normal distribution of cell types. The jaundice subsided within a week. The patient had many subsequent attacks of similar pain during the following years, but jaundice did not recur. She was again admitted to the San Francisco Hospital in 1936 because of a buccal ulcer that developed after the extraction of several teeth. The ulcer healed slowly, and a biopsy from its edge was reported only as "necrotic tissue." At this entry her liver was not palpable, but the tip of her spleen was felt 10 centimeters below the left costal margin. She had a microcytic anemia, and the white cell count was between 1,000 and 3,500 with 50 to 60 per cent lymphocytes. Pentnucleotide did not alter the cell count. Her blood Wassermann reaction was negative but the Kahn reaction was positive.

In the systemic history it was stated that in 1923 a private physician treated her arthritis with "iodides, mercury ointment, and malaria" over a two to three month period. The patient could recall no chills resulting from the "malaria." She denied any knowledge of splenic infection, and stated that her physician made no mention to her of this diagnosis.

The present illness began in 1923 when she first suffered from pain, tenderness, and swelling in the left shoulder. Soon other joints were affected, and the disease progressed so rapidly that within one year of its onset there was partial ankylosis of both hips and both knees. Therapy was, in general, conservatively based upon rest, diet, and salicylate, but for a certain amount of occult infection were not treated. During a 20 year period nearly all of her joints were attacked by arthritis, and it was finally necessary to admit her to Laguna Honda Home.

*Physical Examination* The patient was an elderly white woman with evidence of moderate weight loss. There was no fever. The skin was pale and without abnormal pigmentation. Ears, eyes, nose were negative. The mouth was edentulous, and the tonsils atrophic. There were no abnormal findings in the neck, lungs, or breasts. The heart was of normal size and regular rhythm, a systolic murmur was heard over the entire precordium, a diastolic apical murmur was uncertain. Blood pressure was 150 mm Hg systolic and 70 mm diastolic. A smooth, non-tender liver edge was felt 4 centimeters below the right costal margin. The spleen was firm non-tender, and extended 8 to 9 centimeters below the left costal margin. There were no enlarged lymph nodes. The spine was rigid, with moderate thoracic kyphosis. There was ankylosis of all the joints of the legs with flexion deformity of both knees. The right knee was slightly swollen, warm, and tender. The shoulders and elbows were almost completely ankylosed, the wrists were slightly swollen and stiff and the fingers, which showed marked fusiform swelling and stiffness, were partially contracted.

*Laboratory* Hemoglobin 9.2 gm, red blood cells 3,760,000, white blood cells 1,240 with 32 per cent polymorphonuclear cells, 35 per cent small lymphocytes, 38 per cent large lymphocytes, 2 per cent monocytes. Blood Wassermann reaction was negative, Mazzini positive. Spinal fluid Wassermann negative, Pandy negative, Lange 0000000000. Urine specific gravity 1.017, faint trace of albumin, no glucose or acetone, no casts, 8 white cells per high dry field. Bromsulphonphthalein test showed all dye to be removed from the blood plasma within 20 minutes. Blood non-protein nitrogen level was 31 mg per cent. Congo red test at entry found 56 per cent of the dye remaining in the plasma after one hour, this was repeated six months later at which time 74 per cent of the dye remained in the plasma at one hour. The bleeding time was five minutes, and three platelet counts varied from 90,000 to 120,000. Sternal marrow obtained by puncture was too scant for adequate study. Blood cell counts are shown in table 2.

TABLE II  
Blood Studies of Case 2

| Date     | Hgb*  | Rbc** | Wbc   | Pmn | Band | Small L | Large L | Mono | Eos | Baso |
|----------|-------|-------|-------|-----|------|---------|---------|------|-----|------|
| 6-11-27  | 10.47 |       | 7,200 | 66  |      | 34      |         |      |     |      |
| 2- 2-34  | 12.69 | 4.40  | 6,600 | 54  |      | 42      |         |      | 4   |      |
| 10-17-36 | 8.20  | 3.40  | 1,100 | 35  | 13   | 52      | 12      |      |     |      |
| 10-18-36 |       |       | 1,320 | 36  | 10   | 53      | 11      |      |     |      |
| 10-21-36 | 8.20  | 3.80  | 2,160 | 50  | 43   | 42      | 8       |      |     |      |
| 10-24-36 |       |       | 3,500 |     |      |         |         |      |     |      |
| 10-27-36 |       |       | 2,000 |     |      |         |         |      |     |      |
| 10-29-36 |       |       | 1,900 |     |      |         |         |      |     |      |
| 11- 5-36 | 8.78  | 3.90  | 1,000 | 22  | 5    | 78      |         |      |     |      |
| 3-16-43  | 9.20  | 3.76  | 1,240 | 32  |      | 16      | 50      | 2    |     |      |
| 4- 7-43  | 9.04  | 4.01  | 1,080 | 24  |      | 35      | 38      | 2    |     |      |
| 8-26-43  | 9.24  |       | 1,360 | 26  |      | 38      | 23      | 5    | 6   | 2    |
| 9- 1-43  | 9.04  |       | 880   | 26  |      | 58      | 16      |      |     |      |
| 9-10-43  | 9.63  |       | 470   | 20  |      | 53      | 19      | 7    | 1   |      |
| 9-11-43  |       | 4.85  |       |     |      |         |         |      |     |      |
| 9-13-43  |       |       | 580   |     |      |         |         |      |     |      |
| 9-14-43  |       |       | 920   | 42  |      | 29      | 17      | 9    | 1   | 2    |
| 9-16-43  | 8.33  |       | 1,120 | 41  |      | 29      | 27      | 2    | 1   |      |
| 9-21-43  | 8.33  | 4.07  | 600   | 28  |      | 38      | 26      | 6    | 6   | 1    |
| 9-28-43  | 7.85  |       | 760   | 23  |      | 42      | 28      | 7    |     |      |
| 10-13-43 | 6.90  |       | 740   | 32  |      | 21      | 37      | 5    | 3   |      |
| 10-25-43 | 8.20  | 4.08  | 880   | 52  |      | 7       | 31      | 10   |     |      |
| 11- 4-43 | 6.70  |       | 1,040 | 62  |      | 24      | 12      | 2    |     |      |

\* Hemoglobin in grams per 100 c.c. of blood

\*\* Rbc in millions per cubic millimeter of blood



*Course* Aside from developing a severe decubitus over the sacrum in May, two months after entry, the patient's condition was unaltered until August 25, 1943 when she suffered an attack of severe, sudden epigastric pain that was maximal to the left of the midline and radiated to the left shoulder. The left upper quadrant and spleen were very tender. The patient had a chill, and her temperature rose from normal to 102° F. The fever and pain lasted seven days, the white cell count on the second day was 1,360. Splenic infarction was considered as a likely explanation.

Two weeks later, September 9, 1943, the patient had a sudden onset of severe pain in the right upper quadrant with radiation of the pain to the right shoulder. She stated that this was similar to her previous "gall-bladder attacks." She had moderate nausea and some vomiting. Her temperature fluctuated between 99° and 103° F over the next eight weeks. Colic was severe for the first 24 hours, but the pain was dull and of variable intensity after that. Both pain and tenderness persisted to some degree for two months. She had no jaundice, and the urine remained negative. Her white cell count during these last two months varied from 600 to 1,120. Roentgenograms of the abdomen and excretory pyelograms were negative.

During the first week of November she developed abscesses on the lateral aspect of each arm just above the elbows. These may have been related to hypodermic injections of codeine. Fifty to 100 cubic centimeters of pus were removed from each abscess, culture from this material produced *Staphylococcus albus* and hemolytic *Staphylococcus aureus*. On November 10 the patient became stuporous. This progressed to coma, and she died on November 15 with signs of bronchopneumonia in both lungs.

*Autopsy* Description of the body was the same as that given above except for increased emaciation. *Heart* The size was normal, and the valves were competent. The mitral valve contained several atheromatous plaques. There was some atherosclerosis of the coronary vessels. Microscopically the tissues were normal. *Lungs* The left pleural cavity showed numerous old, fibrous adhesions, especially in the lower portion. The bronchi contained thick, mucopurulent fluid. The right lung was moderately congested, the entire left lower lobe and part of the upper lobe contained numerous confluent zones of consolidation. Microscopically some of the consolidated areas contained small abscesses. *Liver* The liver weighed 1,600 grams, had a smooth capsule but a mottled appearance. The anterior edges were sharp. By microscopic examination the central veins and adjacent sinusoids were widened and filled with blood. In these areas the hepatic cells were necrotic, and there was mild infiltration with leukocytes. Groups of adjacent liver cells contained large fat vacuoles. Those cells near the portal spaces showed little alteration. *Gall-bladder* The wall of the gall-bladder was quite thick, dense, and fibrous. The bladder contained numerous pigment and cholesterol stones and thick, turbid brown bile. The fundus of the gall-bladder was adherent to the upper surface of the first portion of the duodenum where, apparently because of pressure of a large stone, there was a fistula of 1.5 centimeter diameter between the gall-bladder and the duodenum. The gall-bladder was also adherent to the gastro-hepatic omentum, which showed considerable scarring. This scar surrounded the portal vein at the point where it received the splenic vein. The latter vein was greatly dilated throughout its length, measuring between 1.5 and 2.0 centimeters in diameter. No thrombosis was present, and no true obstruction could be demonstrated, but it seemed possible that the scarring might have partially constricted this vessel. *Spleen* The spleen weighed 1,000 grams, was firm, had rounded edges, and much of its lateral surface was adherent to the parietal peritoneum by firm, fibrous bands. The splenic artery was patent throughout, though it was tortuous and moderately sclerotic. There was no evidence of infarction. Microscopically the capsule was normal, the central arteries and arterioles were only slightly thickened, and the lymphoid follicles were small, irregular in outline, and widely scattered. The splenic sinusoids and intermedullary

spaces were moderately filled with blood. There was no unusual degree of reticulo-endothelial proliferation or fibrosis. The pulp contained large numbers of lymphocytes and macrophages, with fewer eosinophiles and neutrophils. *Kidneys* These showed moderate arteriosclerotic changes. *Stomach* There was evidence of moderate atrophic gastritis. *Intestines* There were multiple diverticula of the small bowel. *Endocrine Glands* None of these showed significant pathologic changes. *Aorta* Marked atherosclerosis. *Left Knee Joint* The cortex of the bones was thin, and the cancellous bone extremely soft and fragile. The joint was completely obliterated by connective tissue and bony proliferation, and the patella was fused to the anterior surface of the femoral portion of the joint. Microscopically there was seen a small area where an irregular bit of abnormal joint cartilage remained. There was no evidence of residual inflammatory reaction. *Striated Muscle* (left thigh) The individual muscle fibers were indistinct, and both the longitudinal and transverse striations were absent. The few remaining nuclei were long, thin, and atrophic. *Popliteal Nerve* The nerve consisted mainly of collagen bundles and fat cells. The nerve bundles present were small and atrophic, the myelin sheaths showed considerable vacuolization. *Bone Marrow* Specimens were taken from the femur and vertebrae. That from the femur was composed largely of congested and hemorrhagic fat and contained a few small hemopoietic foci of both myeloid and erythrocytic activity. The spinal marrow was hyperplastic and contained few bone trabeculae and fat cells. The majority of the cells were of the myeloid series, and all stages of development were represented. Many myeloblasts, promyelocytes, and eosinophilic myelocytes were noted. Cells of the erythrocytic series tended to be scattered rather than arranged in the usual foci, and the nucleated red cells varied greatly in appearance. There were a few typical normoblasts, but the majority had larger, round nuclei of less hyperchromatic appearance. Many of these corresponded with megaloblasts. The number of megakaryocytes seemed to be reduced.

*Comment* This patient's arthritis was definitely of the atrophic type, it was chronic, widespread, severe, and associated with progressive emaciation. She had no enlarged lymph nodes, and abnormal pigmentation of the skin was wanting. Microcytic anemia, marked leukopenia, and splenomegaly were persistent during the last seven years of life. The factors that caused the anemia and leukopenia are uncertain, but as in case 1 these findings were associated with a hyperplastic bone marrow that showed evidences of erythrocytic maturation arrest. However, in the present case myeloid hematopoiesis was active in the marrow. A few patients belonging to this general group described by Felty have been subjected to splenectomy because it was thought that the abnormal spleens might have been, in an unexplained manner, responsible for the low white cell circulation and the anemia.

In the present case the leukopenia and splenomegaly developed between 1934 and 1936. In 1933 the patient had frequent attacks of typical gall-bladder colic. Early in 1934 she was studied during one of these attacks that was associated with jaundice. She continued to have occasional bouts of right upper quadrant pain, and this complaint was present rather constantly during her last two months of life. However, the attack in 1934 seems to have been the most severe, and it was the only one during which icterus was present. At autopsy the cholecysto-duodenal fistula appeared to be of relatively recent origin and caused by pressure of a large stone that was still present in the fundus of the gall-bladder. The extreme dilatation

of the splenic vein seemed definitely to be related to the older scarring of the gastro-hepatic omentum to which the gall-bladder was adherent. Pathologic examination of the spleen revealed no abnormality other than typical congestive splenomegaly. It seems logical, therefore, to conclude that the splenomegaly in this case resulted from constriction of the splenic vein by scarring of the gastro-hepatic omentum, the omental scar was an inflammatory reaction to the adherent gall-bladder that had been a focus of chronic infection at least three years before the splenomegaly appeared.

The striated muscle studied in this case is not properly comparable to specimens studied in some cases of chronic atrophic arthritis, for it was taken from the left thigh just above the ankylosed knee joint. Degeneration and atrophy were anticipated findings. The biopsies obtained by Curtis and Pollard<sup>6</sup> from 12 cases of chronic atrophic arthritis were taken from muscle groups remote from affected joints. Their cases were evenly distributed among those with and without splenomegaly and leukopenia. They noted a similar pathologic alteration in nearly all specimens from each group: increase in the interstitial nuclei of the muscle fibers, and small perivascular infiltrations throughout the muscle. They interpreted these changes as evidence that chronic atrophic arthritis is a generalized infectious process rather than a disease that confines its effects to the joints and adjacent peri-articular tissues. This concept has long been accepted by Hench and others.

*Case 3* D. P., 72 year old white American housewife, entered Laguna Honda Home June 19, 1944 because of incapacitating atrophic arthritis. Her family history was without significance. She had taken no drugs, and had used neither alcohol nor tobacco during her life. Aside from common childhood diseases she had no serious illness other than arthritis. Her systemic history contributed no pertinent information.

*Present Illness* In 1911, at the age of 39, she first noted soreness of the feet. Soon the joints of her hands and feet were swollen, red, and painful. Slowly and intermittently other joints were similarly affected. The course of her illness was characterized by remissions and exacerbations of arthritic inflammation. Fifteen years after the onset of her illness her hands and feet became permanently deformed. By 1932 she was bed-ridden and remained so. During these last 12 years she developed severe contractures with increasing skeletal deformity. She followed several dietary regimens without benefit, there was no history of parenteral therapy. In the three months preceding her entry to the hospital her hands, feet, and legs became increasingly swollen, her appetite failed, and she became helpless.

*Physical Examination* An elderly white woman, emaciated, with stiff, contracted extremities. She was afebrile. The skin was dry, loose, and non-pigmented. There were numerous decubiti over the body—on shoulders, hips, and buttocks. Examination of ears, eyes, and nose was negative. Snags of a few teeth remained in the lower jaw. The tonsils were atrophic. There were no palpable cervical lymph nodes. The thyroid was not felt. The thorax was symmetrical, and there were a few moist râles at the left lung base. The heart was not enlarged, the rhythm was regular, and there were no murmurs. The liver edge was firm, non-tender, and was felt just below the rib-cage in the right upper quadrant and in the midline. The spleen was firm, non-tender and extended 6 centimeters below the left costal margin. There were small, hard lymph nodes in both inguinal regions. Rectal and pelvic examinations were not performed. The spine was rigid and had a marked thoracic kyphosis. There was muscular wasting in all extremities, and a slight edema of the

hands with more pronounced edema of the legs and feet. The fingers showed marked fusiform deformity with extreme joint destruction, many of the phalanges of both fingers and toes seemed completely disarticulated. Partial to complete ankylosis was present in the elbows, knees, and hips, flexion contractures were present in all extremities.

*Laboratory* Hemoglobin 5.85 grams, red blood cells 2,510,000, white blood cells 2,040 with 60 per cent polymorphonuclears (8 per cent of which were banded), 9 per cent small lymphocytes, 18 per cent large lymphocytes, 11 per cent monocytes, 1 per cent eosinophiles, 1 per cent basophiles. Platelets 231,000. Blood urea 60 mg per cent. Total blood protein 5.68 gm per cent. Congo red test 86 per cent of dye remained in the plasma after one hour. Urine cloudy, specific gravity 1.018, trace of albumin, no sugar or acetone, occasional hyaline and granular casts, 3 white cells per high dry field.

*Course* On the day after entry the patient slipped from the side of the bed and fractured her left femur. Two days later she developed râles in both lungs, a fever of 102° to 104° F, and died on June 24, 1944. The day before her death the white cell count was 5,160. Because of her fracture a coroner's autopsy was ordered.

*Autopsy* *Thorax* Each pleural cavity contained about 100 cubic centimeters of free fluid. *Lungs* There was a fibrinous exudate over the pleural surface of each lung, evidence of moderate atelectasis, but no sign of pneumonia in the sections studied. *Heart* This organ was moderately enlarged. The coronary arteries were markedly sclerotic, but no evidence of occlusion was noted. The myocardium showed no discrete scarring. *Liver* This was not weighed, but was judged to be one and one-fourth times normal size. The edges were rounded. Microscopically there were no cirrhotic changes, but there was moderate cloudy swelling of the cytoplasm of the hepatic cells. *Spleen* This weighed 700 grams and on gross section was of reddish color, slightly fibrous, and without apparent lymphoid follicles. On microscopic examination the sinusoids were dilated, and there was some swelling and increased prominence of the endothelial cells of the sinuses. There was slight increase in the fibrous tissue elements of the pulp. No siderotic nodules were present. *Kidneys* These were of normal size. There was an exceptional degree of arterial and arteriolar sclerosis. Within the interstitial tissue there was a diffuse lymphocytic infiltration; many glomeruli were fibrosed and hyalinized. *Adrenal Glands* These were normal except for a diffuse hemorrhage in one, this was apparently terminal and the result of rupture of a small, sclerotic vessel. *Bone Marrow* Sections were taken from the vertebrae. These showed mild myeloid hyperplasia with hemopoiesis of myeloid and erythrocytic cell series.

*Comment* This patient was observed for so short a time that thorough study was not possible, however, some conclusions are evident. Her arthritis was definitely of the atrophic type, was widespread, and had been present for over 30 years. She had no marked lymph node enlargement though a few nodes in each inguinal region were palpable. There is no information regarding the time when splenomegaly, anemia, or leukopenia appeared. Her anemia, like that of the previous cases, was microcytic, but it was more severe. No hemorrhagic manifestations were noted, but stool examination and gastrointestinal roentgen-ray studies were not performed. The leukopenia might have been an expression of the degree of anemia, the platelet count, however, was not depressed. The pathological alterations in the liver were moderate and non-scarring. The spleen was slightly congested, but not at all to the degree seen in case 2. These splenic changes

were similar to those of non-specific character described from comparable cases in earlier papers. They will be mentioned below. The bone marrow was slightly hyperplastic, but unlike that of the previous two cases it revealed no evidence of maturation arrest of the cells of either series.

### DISCUSSION

In repeated general statements regarding atrophic arthritis Hench<sup>7</sup> has emphasized that it is not a disease that confines its effects to the joints alone but is a generalized affection that causes such diverse results as general weakness and fatigue, functional disorders of the stomach, wasting of muscles that are remote from inflamed joints, and varied reticulo-endothelial system reaction. He has pointed out that "from time to time various names have been attached to the combination of arthritis in association with alteration in the blood picture and with involvement of one or more parts of the reticulo-endothelial system (lymph nodes, liver, spleen). The so-called Felty's syndrome is the latest such syndrome. Felty himself concluded that the syndrome was probably not a new disease, and others have felt that it is merely another pathologic combination of arthritis and reticulo-endothelial reaction, little different from other syndromes reported by Chauffard (1896), Still (1897), and Herringham (1909), and that a new name is, therefore, unnecessary." Chauffard<sup>8</sup> was essentially interested in the appearance of enlarged, tender lymph nodes in a group of patients with atrophic arthritis, while blood cell counts that were taken from this group were normal. Still's<sup>9</sup> cases were among children who had splenomegaly in addition to their atrophic arthritis and enlarged lymph nodes. His patients had either normal or increased white cell counts. Herringham<sup>10</sup> described a boy with Still's disease who also had extreme hepatomegaly. Felty's cases are mentioned above. No thorough studies of biopsy or autopsy material are mentioned in these reports. Singer and Levy<sup>11</sup> have reviewed extensively the world literature concerned with arthritis in association with varied reticulo-endothelial responses.

In 1942 Talkov, Bauer, and Short<sup>12</sup> reviewed all the cases of Felty's syndrome previously reported and described five new cases that could have been classified in the same group. However, they considered that all of their cases and fully 70 per cent of those cases they reviewed strongly suggested the possibility that an accompanying disease unassociated with the arthritis was responsible for the leukopenia and splenomegaly. Only two of their cases were studied post mortem. Among the other three patients, one died of a massive hematemesis that made it "impossible to exclude cirrhosis of the liver with esophageal varices as the cause not only of the fatal hemorrhage but also of the splenomegaly and leukopenia", one, a girl of 22 who had "apparent rheumatoid arthritis" for 18 months and "slight leukopenia," was subsequently diagnosed as having familial hemolytic anemia, the third had the usual findings of Felty's syndrome when first seen, but when she

was examined four years later "the spleen was no longer palpable, and the leukopenia had vanished, and yet the arthritis had progressed somewhat in severity"

Speculation upon those cases reported without biopsy or autopsy studies is pleasant clinical exercise, but since we are concerned with the problem of whether a circumscribed group of signs is to be interpreted as a syndrome or as the effects of a chance association of two unrelated diseases, it is more profitable to confine discussion to those reports accompanied with pathologists' findings. These will be briefly reviewed.

In 1932 Hanrahan and Miller<sup>13</sup> described a patient who had, in addition to the usual findings, an associated hepatomegaly, urobilinuria, at least one stool strongly positive for occult blood, gastric hypoacidity, and some dyspepsia. Roentgen-ray studies of the gastrointestinal tract were essentially negative. The white cell count varied from 640 to 1,600. A splenectomy was performed, and a biopsy specimen was taken from the free edge of the liver. The spleen weighed 525 grams. Microscopically it showed largely Malpighian bodies and dilated sinuses. The spaces between the sinuses in the pulp were unusually wide and filled with eosin-staining material. The endothelial cells lining the sinuses were enlarged, and the sinuses were filled with large cells showing red cell phagocytosis. Many plasma cells were in the pulp. The liver showed early fatty changes in the central zone with moderate round cell infiltration along the portal vein radicals. This infiltration was limited to the periphery of the lobules where there was a very slight increase in fibrous tissue. It was the pathologist's opinion that these changes are not uncommon in specimens removed from the free edge of the liver. The alterations in the spleen seem non-specific, evidence of chronic congestion is wanting. The patient died 18 months after splenectomy, and, as suggested by Talkov, Bauer, and Short, he may have had cirrhosis of the liver.

Craven,<sup>14</sup> in 1934, reported another case that was subjected to splenectomy. This patient also had a liver that was definitely enlarged, and a bromsulphalein test performed before splenectomy showed 45 per cent of the dye retained in the plasma after 30 minutes and 30 per cent retention after one hour. Eight months after operation there was no dye retention after 30 minutes. Other liver function tests were normal at all times. The microscopic description of the spleen was the same as that noted by Hanrahan and Miller. These changes were regarded as similar to those found in a variety of infectious diseases. A green-producing streptococcus was cultured from a biopsied lymph node. The patient died about 14 months after splenectomy.

Also in 1934 Price and Schoenfeld<sup>15</sup> reported the case of a patient aged 57 who had chronic atrophic arthritis, splenomegaly, pigmentation of the exposed areas of the skin, and a white cell count that varied between 3,100 and 5,300. Liver function tests were normal. The patient was scheduled for splenectomy but died from pericarditis the night before operation. At

autopsy the joints were found to have the typical changes of atrophic arthritis. The liver was normal. The spleen weighed 510 grams and revealed a diffuse fibrosis with dilatation of the splenic sinuses which showed areas of myeloid activity. The spleen was regarded as typical of those described by Ward<sup>16</sup> as chronic septic splenomegaly. In the lungs there were healed and caseating tubercles. It is quite possible that the active tuberculosis in the case was responsible for the leukopenia. It may also have been the cause of the terminal pericarditis and splenomegaly.

Reich<sup>17</sup> reported a case in 1936. The patient was a 21 year old boy who had had "rheumatism" at the age of six. There was no history of subsequent joint pain and no physical evidence of arthritis. He had hepatomegaly and splenomegaly, palpable lymph nodes in the inguinal region, an aortic diastolic murmur, moderate anemia and leukopenia. Sternal puncture was interpreted as showing a "moderate degree of lymphocytic infiltration," and a biopsied lymph node was diagnosed as "chronic catarrhal lymphadenitis." He had a negative blood culture, and all roentgen-rays were negative. He was treated with transfusions and splenectomy. The spleen "was very large and presented the picture of chronic splenitis." The patient died 10 days postoperatively. Reich felt that this patient represented an early stage of Felty's syndrome, and that the causative agent of infection was a *Streptococcus viridans* that could not be isolated. Neither conclusion seems justifiable.

In the same year Singer and Levy<sup>11</sup> described two cases in the course of an extensive review of the problem of etiology in the group of patients described by Still, Chauffard, Herringham, Felty, and others. One of the patients, a man of 55, had typical chronic atrophic arthritis of nine years' duration, he had splenomegaly, enlarged lymph nodes, moderate anemia and leukopenia for at least two years before death. In the last months of illness he was intermittently febrile, had repeated showers of petechial hemorrhages, a blood culture that was positive for *Streptococcus viridans*, and evidence of cardiac decompensation. Subacute bacterial endocarditis seemed evident clinically, though at autopsy his heart wanted any valvular or congenital lesion. The second case was that of a woman aged 49 who was essentially a cardiac patient but who had had atrophic arthritis of the hands for five years. She was observed only during the last four months of life, and enlargement of the spleen was noted only at her final hospital entry two days before she died. When first seen she was treated for acute cardiac decompensation. The following month she developed erysipelas that cleared rapidly. During the last three weeks of illness *Streptococcus viridans* was twice cultured from her blood. She ultimately developed severe chills, an acute sore throat with a yellow-gray membrane over tonsils and pharynx, and agranulocytosis. Her final blood studies showed a red cell count of 1,480,000, hemoglobin 35 per cent, white cell count 450 with 81 per cent lymphocytes and no polymorphonuclear leukocytes. The platelet count was about 42,000. Jaffé performed the autopsies of these cases and submitted

diagnosis of sepsis lenta on each. Both showed evidence of generalized infection. In each the bone marrow revealed active hemopoiesis of erythrocytic and myeloid cells. There was moderate passive congestion of the liver. In the first case, the second showed cloudy swelling and lymphocytic infiltration of the periportal tissue. The heart in the second case had no valvular lesion, but Aschoff bodies were demonstrated in the myocardium. There was no history of rheumatic fever. The spleens weighed 1,710 and 20 grams respectively. Sections of the larger spleen taken from the first case were almost identical with those described by Hanrahan and Miller and by Craven. The smaller spleen showed less cellular hyperplasia of the reticulum but a marked increase in the fibrillar elements, it also contained a large, recent infarct. Cultures made from the spleens yielded a pure growth of *Streptococcus viridans* in the first case and "both a green-producing streptococcus and a hemolyzing streptococcus" from the second case. On the basis of these data and a review of the literature Singer and Levy concluded that cases grouped with Felty's and allied syndromes represent different forms of the same disease, that one disease process is responsible for the varied tissue response noted in these cases, and that the usual etiologic organism is a streptococcus of the viridans type.

Williams<sup>18</sup> also reported a case in 1936. His patient, a man aged 54, had a palpable spleen when first examined. His joint pains had been present for only 10 days, though he had had malaise and intermittent chills over a two month period. He was found to have a polyarthritis, but this was diagnosed by roentgen-ray as of the hypertrophic type. He had a moderate anemia, and his white cell count was between 1,600 and 4,900. Nine weeks after he was first observed he developed an extensive ulceration of the soft palate and tonsillar pillars. At this time his white cell count was 2,500 with 35 per cent polymorphonuclear leukocytes. The ulcers healed shortly. Blood culture was negative. One year later he reentered the hospital because of soreness of the joints and weight loss. By examination no abnormalities of the joints were noted. His white cell count was 3,300 with 55 per cent polymorphonuclear cells. He died of pneumonia. At autopsy there was an organized pneumonia of the lungs from which *Streptococcus viridans* was cultured. The spleen weighed 260 grams. The Malpighian corpuscles were neither large nor distinct, and the sinuses were inconspicuous. The pulp was highly cellular, containing mainly red cells, lymphocytes, and plasma cells. The liver showed hydropic degeneration. The normal architecture of the lymph nodes was obliterated by a diffuse infiltration with plasma cells. There was a moderate erythroblastic and lymphocytic hyperplasia of the bone marrow but with maturation arrest of the neutrophilic series of cells. The final pathologic diagnosis classified this patient's arthritis as of the hypertrophic type, therefore, the case does not properly belong in the group under discussion. The slightly enlarged spleen showed little pathologic alteration and the blood dyscrasia is of uncertain type. It does not seem, as suggested by Talkov, Bauer, and Short, to be a malignant neutropenia.



A case of particular interest was described in 1940 by Steinbrocker and Sesit<sup>19</sup>. The patient was observed intermittently from 1928 until 1936. At the first examination he had a polyarthritis of the atrophic type, this had been present in moderate degree for two years. His spleen was just palpable below the left costal margin. Observations during the following eight years indicated a progression of the arthritis, steady enlargement of the spleen so that the tip ultimately reached the iliac crest, appearance of hepatomegaly and general enlargement of the lymph nodes, and periods of low grade fever. His white cell count varied from 2,400 to 4,700 with an apparently normal differential count, anemia was moderate to severe, and the platelet count upon one occasion was 30,000. His last hospital entry was necessitated by increasing dyspnea and anasarca. He died of apparent cardiac and renal insufficiency. In the eight years, the patient was subjected to multiple laboratory tests that returned normal results. Sputum studies and blood cultures were repeatedly negative, the blood uric acid level was normal until the last few days of life when it was 7.18 to 13.0 mg per cent and the blood non-protein nitrogen was 66 mg per cent, Congo red tests were normal, three lymph node biopsies were described as revealing the "characteristics of chronic inflammation". Complete autopsy was denied, but sections from the spleen and lymph nodes were permitted. These showed "Hodgkin's disease associated with terminal miliary tubercles". Postmortem studies of the joints could not be made, but by clinical and roentgen-ray evidence the diagnosis of atrophic arthritis seemed definite. The anemia and leukopenia may have been related to either tuberculosis or Hodgkin's disease, the splenomegaly was caused mainly by the latter affection.

In 1942 Lockie, Sanes and Vaughan<sup>20</sup> reported two cases, one of which was autopsied. This patient was a woman aged 53 who had had chronic atrophic arthritis since she was 30. At the time of first observation nearly all joints were affected, she was emaciated, had enlarged axillary and inguinal lymph nodes and palpable liver and spleen. Fifteen months before death she had only slight anemia, and her white cell count was 10,000 with a normal distribution of cell types. Nine months later she had a marked microcytic anemia, and the white cells numbered only 4,200. One month before death her hemoglobin was 50 per cent, red cell count 2,500,000, white cells 1,850 with 54 per cent lymphocytes and 19 per cent monocytes. Terminally she developed ulcerations of the mouth. At autopsy the spleen was found to weigh 380 grams. The splenic follicles were small, the red pulp increased, and the sinuses were prominent, distinctly dilated, and had hyperplastic endothelial cells. Moderate red cell phagocytosis was noted. This is similar to the spleen described by Hanrahan and Miller and others. The liver showed some parenchymatous degeneration. Lymph nodes were altered by non-specific, chronic inflammatory hyperplasia. Bone marrow revealed "slight to moderate myeloid hyperplasia with signs of arrest of maturation of the granulocyte and erythrocyte precursors". There were mild inflam-

matory changes in the heart and pancreas This case was regarded as similar to those previously described in which the findings were of non-specific, generalized inflammatory process

Steinberg,<sup>21</sup> in 1942, reported three cases, one of which was treated by splenectomy The patient had lost weight and had become increasingly deformed by her arthritis in the 18 months preceding the operation She had some enlargement of cervical and inguinal lymph nodes, but the spleen was barely palpable The white cell count varied from 1,000 to 2,500 Weight of the spleen was not stated Microscopically the Malpighian bodies were seen to be large, and there were abundant plasma cells throughout Evidence of superimposed disease was not found The patient's white cell count rose to 16,000 immediately after operation, but three weeks later there was a decline in her general condition and in the blood picture Details are not given

In the article previously cited,<sup>12</sup> Talkov, Bauer, and Short reported two cases with autopsy study The first was a woman aged 64 who had had atrophic arthritis for at least 20 years She had some abnormal skin pigmentation, marked weight loss, slight enlargement of the cervical and inguinal lymph nodes, palpable liver and spleen The white cell count varied from 1,500 to 4,300 with a normal differential count, she had a moderately severe microcytic anemia Thorough study of the gastrointestinal tract revealed no lesion Blood culture was negative On the third hospital day she developed fever and pyuria, and *E coli* was found in the urine She failed rapidly, suffered multiple decubiti, otitis media, endophthalmitis of the left eye, and died 38 days after admission to the hospital At autopsy *E coli* was cultured from the heart blood The liver weighed 1,900 grams, and showed parenchymal cell destruction, gas bubbles, and large clumps of bacilli The spleen weighed 675 grams It contained an old infarct, the normal architecture was indistinct, and the widely dilated sinusoids contained clumps of bacilli, in the pulp there were many polymorphonuclear cells, large mononuclear cells, erythrocytes, plasma cells, and occasional large phagocytes containing red cells The lymph nodes were altered by the effects of chronic, non-specific inflammation There were bilateral pyelonephritis, acute and chronic, and acute cystitis Bone marrow showed a moderate red cell hyperplasia, there were many mature polymorphonuclear cells, but only occasional myelocytes The joints showed atrophic arthritis The authors felt that sepsis was the chief cause of death and that the pyelonephritis was chronic with an acute terminal exacerbation They thought the leukopenia was probably related to the arthritis, but stated that "since splenomegaly is not uncommon in patients with chronic pyelonephritis, the changes in the spleen may have been due, at least in part, to the pyelonephritis, which obviously antedated the clinical evidence of its presence" It is not a common belief that splenomegaly is a frequent attendant upon chronic pyelonephritis

Their second case was a woman aged 40 who entered the hospital because of symptoms from a large gastric ulcer She also had crippling

atrophic arthritis, slight generalized lymphadenopathy, splenomegaly, a white cell count persistently below 4,000, and a mild hypochromic anemia. It was established that the splenomegaly and leukopenia were secondary to hepatic disease caused by cinchophen ingestion six years previously. The patient died from peritonitis following perforation of the gastric ulcer. At autopsy the "examination confirmed the suspected cause of death and proved the presence of a healed acute yellow atrophy of the liver, chronic congestive splenomegaly with fibrosis, and rheumatoid arthritis."

### SUMMARY

Three cases of chronic atrophic arthritis associated with splenomegaly and leukopenia have been presented together with the complete autopsy record of each. Twelve similar cases reported with biopsy or postmortem studies were reviewed. From this material certain observations may be made regarding the problem of whether this union of clinical findings represents a syndrome, as originally suggested by Felty, or if the majority of these patients are the victims of at least two coincident and unrelated diseases, as argued most forcefully by Talkov, Bauer, and Short.

The splenomegaly of at least four of these 15 cases was clearly caused by a pathologic process unassociated with the general atrophic arthritis. The first case presented in this paper had amyloidosis. References made to the association of amyloid disease with atrophic arthritis indicate not only that the combination is very rare but that a causal relationship between the two affections has not been established. The second patient described in this report had chronic congestive splenomegaly apparently effected by constriction of the splenic vein by scarring of the gastro-hepatic omentum. The spleen of Steinbrocker and Sesit's case revealed the presence of both Hodgkin's disease and miliary tubercles. The second of the cases presented by Talkov, Bauer, and Short had congestive splenomegaly with healed acute yellow atrophy of the liver. Their first case had a spleen of the type described by Ward as chronic septic splenomegaly, however, the infectious process responsible for the splenitis is indefinite. The spleens of the remaining 10 cases showed a similar alteration that was regarded by most authors as a reaction to a non-specific, chronic infection. The third case described in this paper belongs with this group. These latter cases seem to support the contention of Hench and others that atrophic arthritis is part of a generalized infection that affects many tissues including those of the reticulo-endothelial system. The two patients described by Singer and Levy died with *Streptococcus viridans* septicemia. The spleen of their second case was not definitely known to be enlarged until a few days before death; its enlargement may well have been in response to this specific infectious agent. Their first patient, however, had known splenomegaly at least a year before he showed clinical evidence of septicemia. It is not yet possible to accept the suggestion of these authors that *Streptococcus viridans* infection is the probable cause of the Felty and Still-Chauffard syndromes. Then

cases simply indicate that the presence of chronic atrophic arthritis is not a defense against superimposed streptococcus septicemia

The causes of the leukopenia and anemia noted in these patients remain uncertain. Bone marrow studied in some cases showed hyperplasia with maturation arrest of one or more cell types. Marrow specimens from other patients showed active hematopoiesis, though the clinical course had been marked by severe degrees of anemia and leukopenia. It was for this latter group of patients that Steinberg<sup>21</sup> recommended splenectomy on the supposition that the spleen, through an unexplained mechanism, acted as a barrier between the bone marrow and the peripheral blood stream. No case treated by splenectomy has yet been reported in which the beneficial effects upon the anemia and leukopenia were other than transient, and the post-operative course of these patients was characterized by general decline.

### CONCLUSIONS

1 Present evidence indicates that splenomegaly and leukopenia when associated with chronic atrophic arthritis do not constitute a distinct clinical syndrome

2 In a significant percentage of the cases in this group a pathologic process unrelated to that producing the arthritis can be clearly demonstrated to be responsible for the splenomegaly, the cause of the leukopenia is apparent in fewer instances

3 Thorough clinical observations allied with biopsy and autopsy studies fail, in a majority of the cases, decisively to explain the several features as manifestations either of one pathologic process or as the confusion of two separate clinical entities

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### BIBLIOGRAPHY

- 1 FELTY, A. R. Chronic arthritis in the adult, associated with splenomegaly and leukopenia. A report of five cases of an unusual clinical syndrome, *Bull. Johns Hopkins Hosp.*, 1924, **xxv**, 16
- 2 PORTIS, R. B. Pathology of chronic arthritis of children (Still's disease), *Am. Jr. Dis. Child.*, 1938, **lv**, 1000
- IMRIE, A. H., and AITKENHEAD, A. C. Amyloidosis complicating Still's disease, *Lancet* 1939, **ii**, 421
- CARROLL, J. H., and NELSON, R. L. Still's disease with amyloidosis, *Arch. Pediat.*, 1927, **xliv**, 187
- 3 BELL, E. T. Amyloid disease of the kidneys, *Am. Jr. Path.*, 1933, **ix**, 185
- ROSENBLATT, M. B. Amyloidosis and amyloid nephrosis, *Am. Jr. Med. Sci.*, 1933, **clxxxvi**, 558
- Cabot case record. Case No. 19142, *New England Jr. Med.*, 1933, **ccviii**, 757
- DIXON, H. M. Renal amyloidosis in relation to renal insufficiency, *Am. Jr. Med. Sci.*, 1934, **clxxxvii**, 401
- HARDGRAVE, M. U. F. Retention of congo-red in amyloid disease, *Arch. Path.*, 1933, **vi**, 238

4. SOLOMON, W M Amyloidosis in chronic atrophic arthritis, *Ann Int Med*, 1943, xviii, 846  
     REIMANN, H A, and EKLUND, C M Long-continued vaccine therapy as a cause of amyloidosis, *Am Jr Med Sci*, 1935, cxc, 88
- 5 COLLINS, D H Neutrophil leukopenia with enlargement of liver and spleen in rheumatoid arthritis with a note on the leukocytic blood picture in chronic rheumatism, *Rep Chron Rheumat Dis*, 1937, iii, 49  
     EATON, E R Chronic arthritis A report based on the study of the blood cell count in 250 cases, *Jr Am Inst Homeop*, 1932, xxv, 125.
- 6 CURTIS, A C, and POLLARD, H M Felty's syndrome its several features including tissue changes, compared with other forms of rheumatoid arthritis, *Ann Int Med*, 1940, xiii, 2265
- 7 HENCH, P S Discussion, *Jr Am Med Assoc*, 1933, ci, 2078  
     IBID Chronic arthritis, *Nelson Loose-Leaf Living Surgery*, 1935, iii, 108  
     IBID, and others Present status of the problem of "rheumatism" and arthritis review of American and English literature for 1934, *Ann Int Med*, 1936, ix, 883
- 8 CHAUFFARD, A, and RAMOND, F Des adenopathies dans le rhumatisme chronique infectieux, *Rev de méd*, 1896, xvi, 345
- 9 STILL, G F On a form of chronic joint disease in children, *Med Chir Trans*, 1897, lxxx, 48
- 10 HERRINGHAM, W P Rheumatoid arthritis, *Clin Jr*, 1909, xxxiv, 257
- 11 SINGER, H A, and LEVY, H A Relationship of Felty's and allied syndromes to sepsis lenta, *Arch Int Med*, 1936, lvi, 576
- 12 TALKOV, R H, BAUER, W, and SHORT, C L Rheumatoid arthritis associated with splenomegaly and leukopenia, *New England Jr Med*, 1942, ccxxvii, 395
- 13 HANRAHAN, E M, JR, and MILLER, S R The effect of splenectomy in Felty's syndrome, *Jr Am Med Assoc*, 1932, xcix, 1247
- 14 CRAVEN, E B, JR Splenectomy in chronic arthritis associated with splenomegaly and leukopenia (Felty's syndrome), *Jr Am Med Assoc*, 1934, cii, 822
- 15 PRICE, A E, and SCHOENFELD, J B Felty's syndrome Report of a case with complete postmortem findings, *Ann Int Med*, 1934, vii, 1230
- 16 WARD, G Chronic septic splenomegaly, *Lancet*, 1923, i, 429
- 17 REICH, C A case of Felty's syndrome, *Med Rec*, 1936, cxliv, 448
- 18 WILLIAMS, R H Felty's syndrome report of a case with necropsy findings, *Ann Int Med*, 1936, ix, 1247
- 19 STEINBROCKER, O, and SESIT, M F Chronic rheumatoid arthritis with granuloma of the spleen and lymph nodes in a patient presenting the clinical picture of Felty's syndrome, *New York State Jr Med*, 1940, xl, 1795
- 20 LOCKIE, L M, SANES, S, and VAUGHAN, S L Chronic arthritis, associated with neutrophil leukopenia, splenomegaly, and hepatomegaly, *Am Jr Clin Path*, 1942, xii, 372
- 21 STEINBERG, C L The value of splenectomy in Felty's syndrome, *Ann Int Med*, 1942, xvii, 26

# OLIGURIA AND ANURIA DUE TO INCREASED INTRARENAL PRESSURE\*

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THE author's motive in publishing the results of this investigation was a desire to devise adequate treatment for the great number of victims of crush injury occurring in the war zones. Some weeks before the invasion of France on June 6, 1944, the author sent an extensively documented article to the Headquarters of the Medical Staffs of the Allied Armies which summarized the results of a study begun one year previously (June, 1943). This study led him to recommend a new therapy for two diseases of high mortality frequently occurring in the war zones, crush injury and transfusion kidney. Although the new treatment (which includes bilateral decapsulation of the kidneys) in practically all respects is just the opposite of that recommended in textbooks and current medical journals, an unfavorable reply was received from only one of the Medical Staffs. Subsequently, however, in a letter from the War Office in London, publication of the article was recommended, and later communications stated that the new therapy was accepted and widely used at the time in the British Armies.

The investigation was stimulated by a discussion of the renal lesions in a case of poisoning by mercuric chloride at a Pathological Conference in the Charity Hospital in New Orleans. It seemed to the pathologist conducting the conference and also to the author that no satisfactory explanation had been published for the development of anuria in such a condition as mercuric chloride poisoning, in which there is extensive destruction of tubular epithelium and almost undamaged glomeruli. This is just the reverse of what might be expected when the reabsorptive mechanism is destroyed. It seemed to the author that hitherto insufficient attention had been paid to changes in intrarenal pressure. The question arose, could a change (increase) in intrarenal pressure cause oliguria and anuria?

It seemed practically impossible to devise a satisfactory experiment to test this point in a living mammal. Since urine secretion is believed to be in considerable part a mechanical filtration process, the author constructed a mechanical device ("artificial nephron") by means of which conditions believed to be present in the kidney can be imitated and controlled. The conclusions reached in this article are based in part on observations made with this artificial nephron and in part on a study of autopsy material.

The symptom complex which, the writer believes, results from increased intrarenal pressure, is characterized by oliguria or anuria with consequent hyperazotemia and uremia. The mortality is high, and may reach 65 per

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cent in transfusion kidney and nearly 100 per cent in crush injury. For the sake of convenience and brevity the symptom complex will subsequently be referred to as "the syndrome."

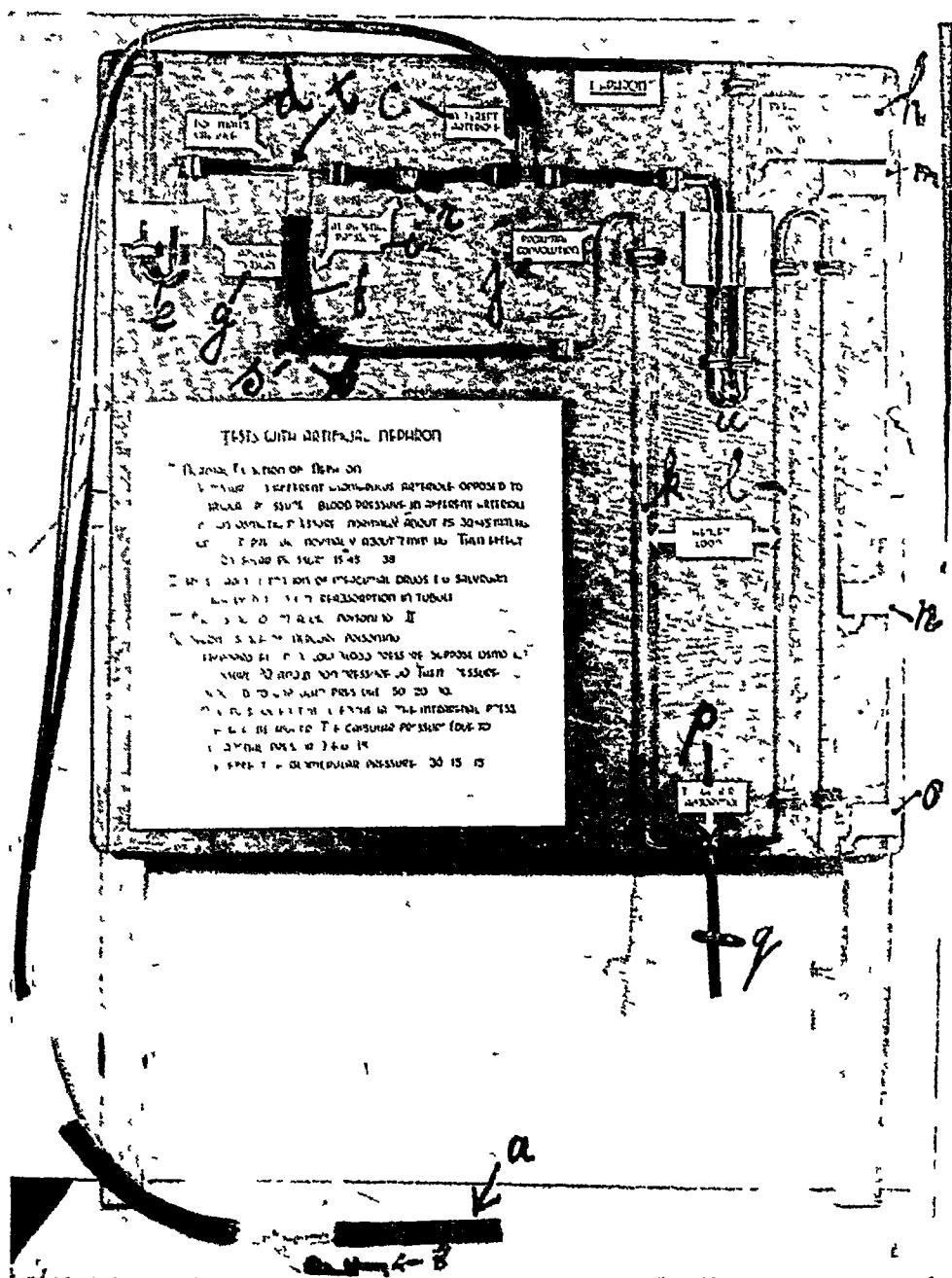
The primary factor which makes possible a significant rise in intrarenal pressure is the fact that in adult human beings and in certain animals like the dog and cat, the renal capsule is relatively rigid and inelastic. A relatively slight increase in the bulk of the intracapsular renal tissues may, therefore, cause a significant rise in intrarenal pressure. In small children, on the other hand, and in some animals such as the guinea pig, in which the capsule is relatively elastic, it is probable that the syndrome can not develop.

Among the pathological disturbances which may cause an increase in bulk and a rise in intrarenal pressure are edema, exudate, or neoplastic infiltration of the interstitial tissue, swelling of the tubular epithelium, and dilation of the tubules. The latter may be caused by obstruction of the tubules by solid casts (of necrotic tubular epithelium, hematin, myoglobin, Bence-Jones protein, sulfonamide crystals). These obstructions may be present in the dilated tubules but often they are present in parts of the tubules distal to the areas of dilatation. It is not so much the mechanical obstruction to the outflow of urine which causes the anuria, as the resulting increase in intrarenal pressure. The syndrome may develop in cases in which only part of the tubules is obstructed, or in which no obstruction can be demonstrated. Another relatively benign and transient cause is dilatation of the intrarenal blood vessels as in chronic passive congestion. This may explain the oliguria of congestive heart failure (vide infra).

Such changes are seen in the kidneys not merely in mercuric chloride poisoning, crush syndrome and transfusion kidney, but, in some cases in a large number of other diseases<sup>30</sup>. The same syndrome may be anticipated in these conditions, and further studies along this line are in progress. Associated lesions of the glomeruli may occur, but this does not play an essential part in producing the syndrome. Uremia due to glomerular injury is an entirely different process and must be sharply differentiated.

*Dynamics* The artificial nephron (figure 1) is constructed of glass and rubber tubes connected with two mercury manometers and provided with several clamps to control pressure and rate of inflow. Tube c, representing the afferent arteriole, is connected with a water tap to imitate inflowing blood. By adjustment of the water-inflow and of clamp r, the pressure in the afferent arteriole, as measured in manometer u, can be adjusted to any desired level. The effective filtration pressure in Bowman's capsule (tube d) is controlled by clamp s, and measured by manometer e. The proximal convoluted tubule (j), Henle's loop (k and l), the distal convolution (m), and the collecting tubule (n) are represented. The outflow of water at o represents urine discharged into the ureter. By adjusting clamp q, a trickle of water can be provided to imitate that reabsorbed by the tubules. Imitation of the malpighian body by a device containing a separating membrane which allowed the filtration of water freely did not change the result. Such a mem-

brane is, therefore, superfluous and merely makes the construction somewhat more complicated



**FIG 1** Artificial nephron See description in text

**Normal Intratubular Pressures** The following figures are estimations for man and are deduced from measurements made on isolated blood-perfused kidneys of dogs (Winton<sup>1</sup>). With a normal blood pressure in the brachial artery, the blood pressure in the afferent arteriole is about 75 mm



Hg The osmotic pressure in this vessel is normally about 30 mm Hg. The difference, indicating the pressure opposed to the pressure in Bowman's capsule ("capsular pressure") is, therefore, 75-30, or 45 mm Hg. The capsular pressure is normally about 5-7 mm Hg. The effective filtration pressure or actual driving force will, therefore, be 45-5 or 40 mm Hg.

*"Normal" Function* When the pressures in the artificial nephron were adjusted to correspond to these normal figures, there was a slow drop-by-drop outflow of water representing the urine from the collecting tubule passing toward the bladder (figure 1, 0) and another outflow from that part of the tubes which represents the places of reabsorption (figure 1, p 223)

*"Abnormal" Function* Examples of abnormal function are imitated by a consideration of the diuretic action of mercurials. Blumgart<sup>2</sup> in 1934 and Walker<sup>3</sup> in 1937 found that salyrgan causes a diuresis in spite of an unchanging rate of glomerular filtration. This mercurial, therefore, must act by reducing the tubular reabsorption of water. By imitating this in the nephron with the aid of a clamp (q), there is an immediate polyuria, in spite of the fact that the rate of supply of water from the tap has not changed.

The first stage of mercury poisoning may be marked by a polyuria, which may be explained on the same basis as that following mercurial diuretics.

The second stage of mercury poisoning is marked by an oliguria or anuria which has been a matter of speculation and controversy for over a century. In mercury poisoning there are probably several factors which contribute to produce the oliguria or anuria, but the principal factor, as in all other diseases which show the syndrome, is increased intrarenal pressure. The old theory which attributed this to mechanical blockage of the tubules by detached necrotic cells is entirely inadequate. Within a week the tubules may be clear of detritus, yet show a degree of dilatation which is apparently sufficient to raise the intrarenal pressure and inhibit urine flow. Two other factors of less importance may play a rôle in the process. If the blood pressure is low, as it may be in mercury poisoning, the syndrome may develop after a smaller rise in intrarenal pressure than would have been required with a normal blood pressure. A hypoproteinemia, which is not rare in mercury poisoning, would tend to prevent the development of the syndrome by lowering the osmotic pressure.

These points may be best illustrated by a hypothetical example. Assume that with a lowered blood pressure in the brachial artery, the pressure in the afferent arteriole may be 50 mm Hg (instead of about 75 mm) and the osmotic pressure may be 20 (instead of about 30 mm) as a consequence of hypoproteinemia. The difference, 50-20, or 30 mm Hg, indicates the pressure opposed to the capsular pressure. The latter, as a result of the increased intrarenal pressure, may be 25 mm Hg (instead of the normal 5-7). If the pressures in the artificial nephron are so adjusted that the manometers read 30 and 25, respectively, the "polyuria" disappears and is replaced by "oliguria" and later by anuria. The same happens if the blood pressure in

the afferent artery is normal, provided the intrarenal pressure is sufficiently increased

If the pressures in the apparatus are so adjusted that the effective filtration pressure is near the critical level, a rise or fall of a few mm of Hg in the intrarenal pressure will result in "anuria" on the one hand, or a free flow of fluid on the other. This "anuria" appears without the introduction of any obstruction in the tubules, such as might be imitated by the application of a clamp to one of the tubes. It is exclusively the result of an increased intrarenal pressure.

*Pathological Findings* In all cases of the syndrome a high tension of the renal capsule is probably present. This may be demonstrated at autopsy provided the latter is carried out very shortly after death, before rigor mortis has set in. Morrison<sup>4</sup> has reported three cases of crush injury which came to autopsy before rigor mortis, in all of which the cut edges of the kidney bulged out over the capsule. The same observation was made in the case reported by the author, and illustrated in figure 3.

The pathological lesions in the kidney which may cause the increased intrarenal pressure, have already been mentioned. In the case of crush injury (and probably in some other diseases) the swelling of the tubular epithelium is probably caused by some toxic substance ("nephrotoxin") liberated by the damaged tissues.

Brief reports of five patients who died with the syndrome follow, together with illustrations showing the pathological lesions in the kidneys. With the exception of the case of crush injury which occurred in California, all the cases came to autopsy in the Charity Hospital of Louisiana at New Orleans. Most of these show that the tubules are more or less displaced either by an interstitial edema with or without signs of inflammation or by neoplastic tissue. Some sections show only swelling of the tubular epithelium. In some cases, however, other sections of the same kidney may show interstitial edema. Occlusion of tubules by blood clots or cell detritus may be completely absent in cases dying of the syndrome.

Figure 2 is a kidney section of a patient 35 years of age who became suddenly ill on October 14, 1944 with high fever and malaise and who died seven days later in uremia. No pyogenic infection was found during life or at postmortem examination. No definite diagnosis could be made, even at autopsy, except that it was probably a virus infection. A cause for the oliguria and anuria which preceded the uremia and for the uremia itself was not found. The lungs showed an interstitial pneumonitis with the well-known hyaline membrane, lining the alveoli. The author could not find a description of a similar alveolar lining in other virus infections than the fulminant form of influenza. In these forms of influenza which the author also saw in Holland in 1918, there is often an abundance of inflammatory edema, not only in the lungs (interstitial pneumonitis) but also in other organs. In this case it was present in the kidneys (interstitial nephritis), undoubtedly

causing an increase of the intrarenal pressure sufficient to produce the syndrome

Figure 3 represents the picture of a kidney section of a patient who died from crush injury in November 1944 as victim of an airplane crash in Cali-



FIG 2 Kidney section of a case which showed the syndrome, in consequence of an interstitial nephritis (part of a fulminant form of influenza) Notice the inflammatory edema, considered the cause of an increased intrarenal pressure, in the interstitial tissue. There were no true obstructions of the tubules, which proves that obstructions may be completely absent in anuria

fornia His left leg was squeezed in the remnants of the airplane for five hours The autopsy report stated "On section of the kidney the cut edge everts and the cortex is raised above the surface of the capsule, as well as the medulla and pyramids" Figure 3 shows the enormous swelling of the tubular epithelium, but according to the report there was also found edema of

the interstitial tissue about the collecting tubules. The picture corresponds completely with the description by British pathologists of such cases of crush injury before the new treatment was applied.

Figure 4 represents a kidney section of a patient, a white female 40 years of age, who had lymphomatosis (Kundrat's lymphosarcoma). Lymphomata were found in many organs, including the renal interstitial tissue. The



FIG 3 Kidney section of a case which showed the syndrome, in consequence of a crush injury (airplane crash). Notice the intense swelling of the tubular epithelial cells. This swelling is considered the cause of an increased intrarenal pressure.

tubules were displaced by lymphomatous tissue. The patient showed an oliguria and a non-protein nitrogen of 235. After three weeks she died from pressure anuria. This demonstrates that neoplasms may cause the syndrome, if their presence between the tubules causes increased intrarenal pressure without any significant damage to the tubular epithelium or glomeruli and without interstitial edema.

Figure 5 represents a section of the kidney from a patient who committed suicide with mercuric chloride. The principal features are described in the legend.

Figure 6 represents a section of the kidney of a patient who died following a transfusion of incompatible blood. The old explanation which attributed the anuria to the blood casts has already been rejected by many pathologists because these casts are often negligible in amount in fatal cases. Boyd<sup>5</sup> stated "It seems probable that there is some other explanation." The most important features are described in the legend.

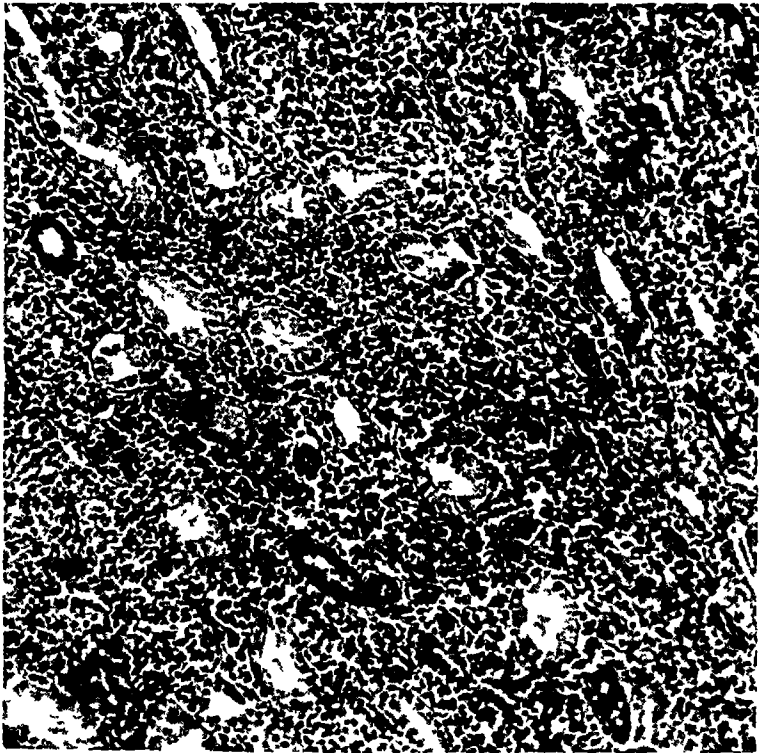


FIG. 4 Kidney section of a case which showed the syndrome, in consequence of lymphosarcomatous tissue in the renal interstices which is considered the cause of an increased intrarenal pressure. No cellular swelling or obstructions.

*Differential Diagnosis* The "malignant pressure oliguria" which constitutes a part of the syndrome under discussion must be differentiated from a "benign pressure oliguria" which is caused by renal stasis, e.g., in heart failure. The latter does not lead to pressure uremia, as far as we know at the present time. Various explanations, none of them satisfactory, have been offered for the oliguria of congestive failure, including increased colloid pressure in the blood vessels, an alteration of the permeability of the invaginated part of Bowman's capsule, as a result of anoxia, and slowing of the circulation through the glomeruli. Although one or more of these factors may contribute to the oliguria, the main cause, the writer believes, is an increase of the intrarenal pressure caused by the dilatation of the veins. This oliguria may be called "benign" because it is reversible spontaneously or

under the influence of digitalis or diuretics With disappearance of general venous stasis the intrarenal pressure decreases to a normal level and normal urine flow is restored

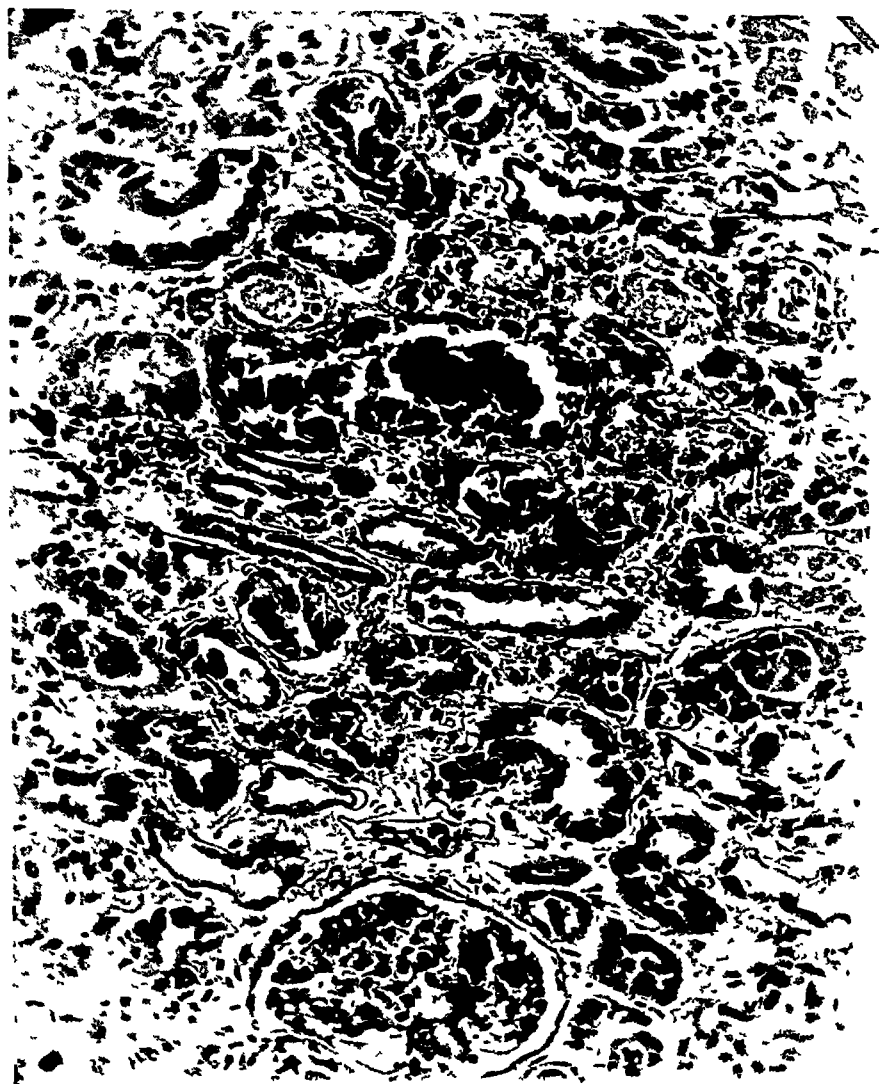


FIG 5 Kidney section of a case which showed the syndrome, in consequence of mercury poisoning Notice the dilatations of the tubules by detritus of blood and desquamated cells, with here and there precipitates of calcium, or dilatation without detritus caused by obstruction in lower parts of the tubules These dilatations of the tubules are considered the cause of an increased intrarenal pressure (Such obstructions are only present in parts of the kidney and therefore *completely insufficient* to explain the anuria )

To differentiate pressure uremia from the uremia of glomerular nephritis is usually not difficult unless both are present in the same patient The typical picture of the syndrome, the history and the clinical evidence of a disease<sup>50</sup> which may cause it, will usually be sufficient to exclude a glomerular uremia The blood pressure is too variable to be of value The usual renal function

tests are also unreliable, because they can not detect beginning renal injury during oliguria. Study is in progress regarding a renal function test which is reliable in cases of oliguria and which is easier than the Iodo-secretory Index, the results of which are also reliable in oliguria (Peters<sup>9</sup>)

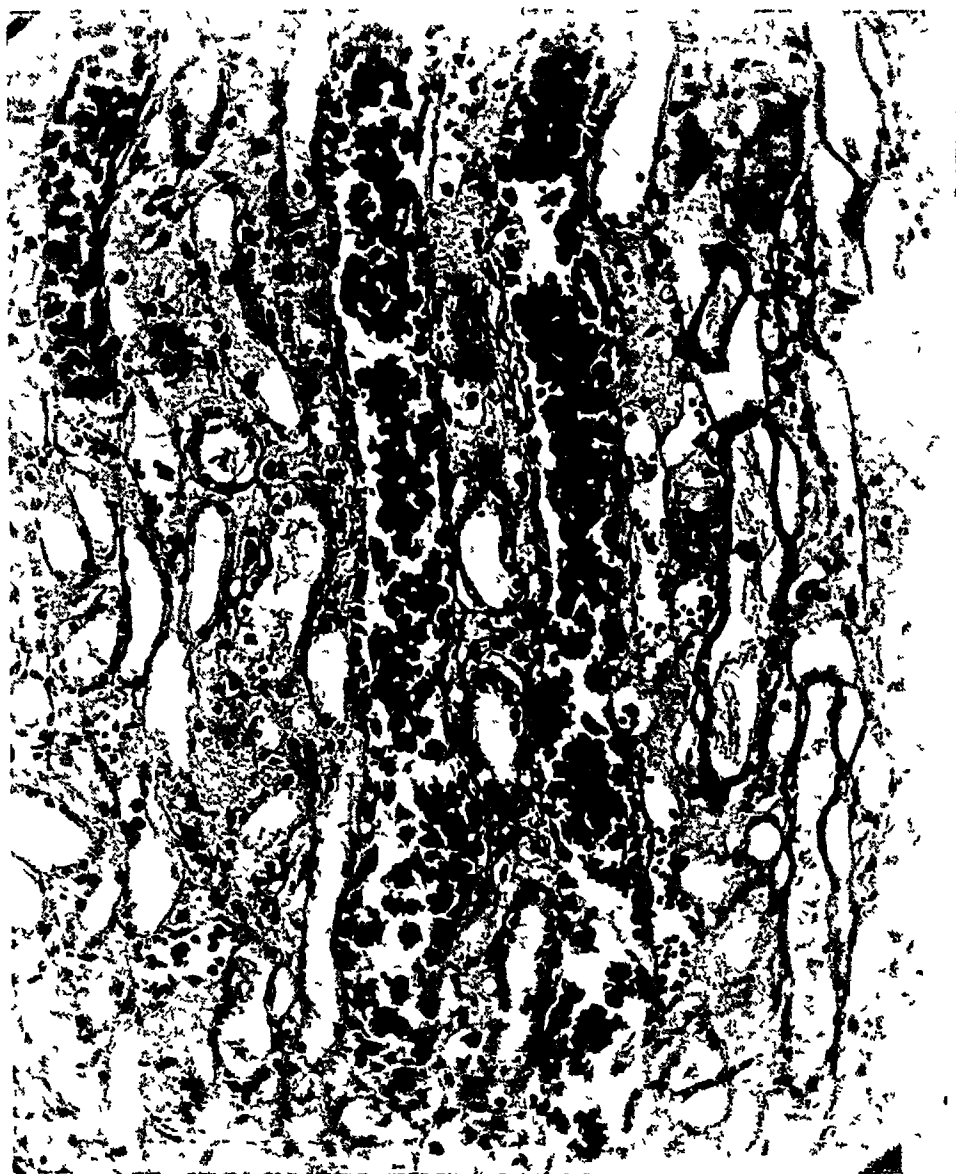


FIG 6 Kidney section of a case which showed the syndrome, in consequence of a blood transfusion (incompatibility). Notice the dilatations of tubules by detritus of blood and desquamated cells. These dilatations and additional dilatations above the points of obstruction are considered the cause of an increased intrarenal pressure. (Such obstructions are present only in a part of the kidney and therefore *completely insufficient* to explain the anuria.)

In the next part of this article only the Transfusion Kidney, the Crush Injury and their therapy will be discussed.

*Transfusion Kidney* This name includes, by definition, the disease syndrome which may follow a mismatched blood transfusion. The symptoms

of Transfusion Kidney need no description here Bordley<sup>7</sup> described an interesting series of 17 cases, in all of which suppression of urine was the outstanding feature, always associated with hyperazotemia Of this group of patients 11 died and six recovered a mortality rate of 65 per cent Navasquez<sup>8</sup> writes, in 1940, that he disagrees with all the explanations of the oliguria or anuria which he found in the literature and he adds that further investigations are desirable

*Crush Injury* During the Messina earthquake of 1908 many of the 65,000 dead died from Crush Injury, as may be concluded from an article written by Colmers,<sup>9</sup> head of a Relief Expedition In 1916 Frankenthal described the symptoms of Crush Injury in soldiers during the first World War It was the result of a mine explosion In March 1941 Bywaters and Beall<sup>10</sup> published the first paper about Crush Injury, observed during the terrible bombardments of London, about September 13, 1940 They call it erroneously "a hitherto unreported syndrome" About 5 per cent of all casualties during large air raids in urban areas appear to be Crush Injuries The flying bomb, especially the noiseless type, has increased its number The symptoms need no extensive description here On admission to the hospital the patient who has usually been buried for several hours, with pressure on a limb, appears in good condition, except for swelling of that limb However, there is often (not always) present a "pre-shock period" which may be discovered by the presence of a hemoconcentration, preceding the fall of the blood pressure The hemoconcentration may reach figures of 22 grams per cent hemoglobin, corresponding to a plasma volume of about one liter If the symptoms of shock disappear with or without therapy, one often observes the symptoms of the syndrome These symptoms are independent of the precedent shock, because cases of Crush Injury are described without shock Morison<sup>1</sup> described three such cases without shock, all three with fatal result Most of the victims were buried under debris between three and 12 hours The existence of a nephrotoxin, formed in the crushed muscles, seems to be admitted by most of the investigators In dogs whose limbs were crushed, mitochondrial changes are found in the tubular epithelial cells, suggesting the action of a nephrotoxin (Eggleton et al<sup>11 12</sup>)

*Prognosis* Bywaters<sup>13-14</sup> in 1942 stated "About one-third of the patients with crush injury have recovered, but these were only minor cases without severe shock or without uremia" From this statement one may conclude that nearly all patients with a fully developed crush injury, including uremia, will die This is in accordance with the observations of Broster and of Patey Broster,<sup>15</sup> in 1943, wrote regarding the therapy of crush injury "There is not much that can be done" and "Few survive when the syndrome is marked" Patey<sup>16</sup> wrote "Most surgeons have had the distressing experience of seeing their patients (with crush injury) pass from a good general condition to death from anuria, despite heroic measures to re-establish the urine flow"



*Treatment* In all diseases associated with this syndrome an attempt should be made as soon as possible to decrease the high intrarenal pressure which is the cause of the anuria or oliguria

Of the older methods of treatment, the following are contraindicated because they are positively or potentially injurious 1 Administration of large amounts of fluid 2 Protein starvation 3 Massive doses of protein 4 Intermittent pressure on the crushed limb 5 Injections of salyrgan 6 Injections of adrenal cortical extract

The administration of large amounts of fluid has been extensively employed, without benefit For example, Younge<sup>17</sup> described a case of transfusion kidney in which the daily urinary output remained between 50 and 100 c c in spite of daily injections of three liters of 2.5 to 10 per cent glucose solution Dunn<sup>18</sup> described the case of a girl of 18 who developed the symptoms of crush injury after being pinned under a beam for six hours during an air raid In spite of a fluid intake of about 3600 c c per day, the urine output was only about 250 c c, and she died after a few days in uremia The author observed a white woman, 43, who developed anuria and died in uremia in spite of the administration of not less than seven liters of fluid a day The autopsy revealed an interstitial nephritis with marked edema of the renal interstitial tissue One may assume that the administration of excessive volume of fluid tends to build up or increase a renal interstitial edema, and thus hampers recovery Wakeman<sup>19</sup> observed the syndrome in several cases of blackwater fever in West Africa Later in this country he observed a case in a girl of 20 who had taken large doses of quinine After her condition had become critical and the non-protein nitrogen had risen to 237 mg per cent, he stopped all fluids, and she immediately improved and finally recovered Although this may have been purely a coincidence, the observation should be kept in mind The author many years ago pointed out the danger of injections of large amounts of fluid in oliguria or anuria Styron and Leadbetter<sup>20</sup> in 1944 stated "A frequent mistake in the therapy (of anuria) is the aimless administration of intravenous fluid"

The administration of alkali in cases of transfusion reaction was recommended by Baker and Dodds<sup>21</sup> in 1925, with the object of preventing the deposition of acid hematin in the renal tubules in cases of transfusion reaction It is now known that obstruction of the tubules with hematin is not essential for the development of the syndrome, since fatal cases of transfusion reaction have been reported without hemoglobinuria (Bancroft<sup>22</sup>) and with persistently alkaline urine without alkali administration (Navasquez<sup>8</sup>) The alkalization of the urine is apparently harmless but superfluous

The treatment recommended consists of 1 Bilateral decapsulation of the kidneys 2 Restriction of fluid intake 3 Administration of certain diuretics 4 Administration of drugs to raise blood pressure, if the latter

is low These measures should be carried out early, as soon as the syndrome is diagnosed

1 Bilateral decapsulation In experiments on animals it has been shown that this procedure reduced the intrarenal pressure by about 50 per cent There is no good reason to suppose that this would be less in the human being This would probably be more than enough to abolish the oliguria in man

Decapsulation was first performed by Harrison (1896) Edebohl (1901) reported the successful use of the procedure in 18 cases, without a death (according to Da Costa <sup>23</sup>) Among others who have used and recommended decapsulation in cases of acute or chronic nephritis with anuria, may be mentioned Talma (1908), Bessesen <sup>24</sup> (1924), Warbasse and Smyth, <sup>25</sup> and Bickham <sup>26</sup> All of these used it only as a last resort measure, after the usual conservative measures had failed and the patient was in a highly critical condition The fact that successful results were obtained, even under such unfavorable conditions, would indicate that bilateral decapsulation is not a dangerous operative procedure

Bancroft <sup>22</sup> was probably the first who performed a decapsulation in transfusion kidney (1925), but he had used "every therapeutic aid that he knew of, before performing this surgical intervention" On the eighth day of oliguria (30 c c urine per day) the blood urea nitrogen was 64 mg per cent, the serum calcium was 4.8 mg per cent, and tetany was present He did the decapsulation on the ninth day when the patient was in extremis Immediate relief followed, and the patient recovered completely Another successful case was reported by Young <sup>17</sup> in a woman of 33 after a transfusion reaction, also as a last resort measure He described the capsule as extremely tense

Talbott <sup>27</sup> studied the effect of unilateral decapsulation on the fourth day of anuria in a woman suffering from a transfusion kidney Catheters were inserted in both ureters Urine flow was established 24 hours later As there was no difference between the urine volumes from the two kidneys and as there was no striking difference in the function of the two kidneys, tested separately six weeks later, he interpreted this "as implying that unilateral decapsulation had no beneficial action on renal function" It seems possible, however, that the operation did cause a resumption of urine flow in the decapsulated kidney, and that this was soon sufficient to cause a little decrease of the interstitial edema and intrarenal pressure in the other kidney

The writer believes both kidneys should be decapsulated as soon as the syndrome can be established, by the presence of oliguria (or anuria) and hyperazotemia It should not be used merely as a last resort measure If done promptly, the risk of operation is much less, and unnecessary damage to the kidneys and other organs can be avoided

The reasons for restriction of fluid intake have been discussed It is probable that burdensome restriction is unnecessary and that enough fluid may be allowed to satisfy thirst

Most of the diuretics have been tried without success. Henderson,<sup>28</sup> however, has reported recovery of a case of crush injury following the intravenous injection of isotonic solution of sodium sulfate. It seems possible that its action may have been due to drawing fluid from the interstitial tissue into the tubules by its osmotic pressure. Although this result may have been accidental, it seems worthy of further trial, especially with slight hypertonic solutions.

The administration of caffeine and coramine is recommended to raise the blood pressure in cases with hypotension. This will help to counteract the effect of the increased intrarenal pressure.

As a means of preventing the development of the crush syndrome, Patey's suggestion<sup>29</sup> to bandage the crushed limb immediately after liberation deserves consideration. By loosening the bandages very slowly after the patient is transferred to a hospital, a *gradual* restoration of the circulation through the crushed tissue will take place and the "nephrotoxin" consequently will reach the kidneys in lower concentration. This is supported by two observations. First, Eggleton et al.<sup>11-12</sup> found that in experiments on cats with crushed limbs, the creatinine tolerance remained normal if the circulation were readmitted slowly, whereas it was decreased if this were done abruptly. Second, it was observed that in patients who were buried longer than 12 hours, the syndrome often did not appear, probably because the circulation could not be restored quickly.

### SUMMARY

1 A syndrome consisting of oliguria or anuria, hyperazotemia and uremia, with a high mortality rate, is described.

2 The syndrome may be present in many different diseases.<sup>30</sup>

3 The primary cause of the oliguria or anuria is a decrease of the effective filtration pressure as a result of an increased intrarenal pressure.

4 The intrarenal pressure can be increased by dilatation of part of the tubules, by interstitial edema, by inflammatory exudate, by swelling of the tubular epithelial cells, by interstitial neoplasms, etc. Dilatation of a part of the tubules may be caused by obstructions, either at or below the areas of dilatation. The obstructing substances may be detritus of tubular epithelial cells or of blood cells, crystals, or certain types of casts. Swelling of the cells, interstitial edema or exudate presumably can be produced by toxic substances which may develop within the body or be introduced.

5 Experiments with an artificial nephron demonstrate that an increase of a few mm Hg, in the intrarenal pressure, may cause "oliguria" or "anuria." A slight reduction of an increased intrarenal pressure (which can easily be obtained in vivo by decapsulation) promptly restores the normal "urinary output." It is estimated from animal experiments that bilateral decapsulation decreases the intrarenal pressure by about 50 per cent, which is undoubtedly more than sufficient to restore a normal urinary output.

6 The therapy previously employed did not reduce the mortality rate of a fully developed syndrome below nearly 100 per cent in crush injury, below 65 per cent in transfusion kidney, or below 60 per cent in many of the other diseases associated with the syndrome. This old therapy, founded on wrong conceptions as to the etiology, probably often hampers recovery by producing or increasing interstitial renal edema.

7 The therapy proposed for the syndrome in any disease in which it occurs, should be instituted immediately after it appears. It consists of one or more of the following procedures: 1 Emergency bilateral decapsulation. 2 Restriction of fluid intake. 3 Administration of certain suitable diuretics. 4 Administration of drugs which raise the blood pressure in cases with low blood pressure. In severe cases all four procedures may be necessary.

8 An emergency decapsulation in severe cases associated with the syndrome, is more urgent than an appendectomy in acute appendicitis because the average mortality is much higher in the former than in the latter. A decapsulation will seldom do harm, in the hands of a competent surgeon.

9 Diseases associated with the syndrome should be admitted as emergency cases on a surgical ward.

The following quotation is from a letter from one of the Editors of *The Lancet*, who read the article sent by the author to the Medical Staff of the British Army in June 1944:

"You are no doubt right in urging that the raised intrarenal pressure is the basis of the transfusion and crush kidney, and that this can best be treated by decapsulation. The treatments which you recommend—decapsulation, diuretics, and pressor drugs—are now widely used, separately or in combination."

The author would appreciate receiving short reports of cases treated by this method.

#### BIBLIOGRAPHY

- 1 WINTON, F. Physical factors involved in activities of mammalian kidney, *Physiol Rev*, 1937, **xvii**, 408.
- 2 BLUMGART, H. et al. Action of diuretic drugs, action of diuretics in normal persons, *Arch Int Med*, 1934, **liv**, 40.
- 3 WALKER, A. et al. Renal blood flow, etc, *Am Jr Physiol*, 1937, **cxviii**, 95.
- 4 MORISON, J. Physiology of streptococci, etc, *Jr Path and Bact.*, 1941, **liii**, 1-12.
- 5 BOYD, W. Textbook of pathology, 1944, Lea-Febiger, Philadelphia, p. 603.
- 6 PETERS, J. T. Estimation of the renal function, etc, *Arch Int Med.*, 1941, **lxvii**, 345.
- 7 BORDLEY, J. Reactions following transfusions of blood, *Arch Int Med*, 1931, **xlvi**, 288.
- 8 NAVASQUEZ, S. The excretion of hemoglobin, *Jr Path and Bact.*, 1940, **li**, 413.
- 9 COLMERS. Erdbeben in Messina, *Arch f klin Chir.*, 1909, **xc**, 701.
- 10 BLYWATERS, E., and BEALL, D. Crush injuries, *Brit. Med Jr*, 1941, **xxii**, 427.
- 11 EGGLETON, M. et al. Impairment due to crushing limbs in dogs, *Brit. Med Jr*, 1942, **ii**, 392, 459.
- 12 EGGLETON, M. et al. Renal damage due to crush injury, *Quart Jr Exper Physiol*, 1943, **xxxii**, 89.
- 13 BLYWATERS, E. War medicine series crushing injury, *Brit Med Jr*, 1942, **ii**, 643.
- 14 BLYWATERS, E. Ischemic muscle necrosis crushing injury, *Jr Am Med Assoc.*, 1944, **ccxli**, 1103.
- 15 BROSTER, L. Symposium on war wounds, crush or compression injuries, *Med Press*, 1943, **ccii**, 78.

- 16 PATEY, D, and ROBERTSON, J Compression treatment of crush injuries, *Lancet*, 1941, i, 780
- 17 YOUNGE, P Two unusual transfusion reactions, *New England Jr Med*, 1936, ccxiv, 879
- 18 DUNN, J et al Crush syndrome, *Lancet*, 1941, ii, 549
- 19 WAKEMAN, A et al Metabolism and treatment of blackwater fever, *Am Jr Trop Med*, 1932, xii, 407
- 20 STYRON, CH, and LEADBETTER, W The treatment of anuria, *New England Jr Med*, 1944, ccxxx, 721
- 21 BAKER, S, and DODDS, E Obstruction of renal tubules, *Brit Jr Exper Path*, 1925, vi, 247
- 22 BANCROFT, E Anuria following transfusion, *Ann Surg*, 1925, lxxxi, 733
- 23 DA COSTA, J Modern surgery, 1931, Saunders, Philadelphia, p 1213
- 24 BESSERFN, D Renal decapsulation, *Am Jr Surg*, 1924, xxxviii, 264
- 25 WARBASSE, J, and SMYTH, C Infections and inflammations of the kidney, *Surg Treatment*, 1937, iii, 122
- 26 BICKHAM, W Renal decapsulation, *Operative Surgery*, 1930, v, 379
- 27 TALBOTT, J Medical progress, *New England Jr Med*, 1942, ccxxvi, 228
- 28 HENDERSON, R Recovery from crush injury, *Brit Med Jr*, 1941, ii, 197
- 29 PATEY, D First aid treatment of compression syndrome, *Brit Med Jr*, 1942, ii, 212
- 30 Thirty-four diseases, in which the syndrome may appear, are mentioned in an article that will be published in the *Acta Medica Scandinavica* (Stockholm), in the near future. More extensive discussion about these diseases, with quotation of examples, will be published later.

# CASE REPORTS

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## THROMBOCYTOPENIC PURPURA FOLLOWING THE USE OF SULFATHIAZOLE \*

By PAUL S STRONG, Major, M C, and EDWARD M GLASSBURN,  
Captain, M C

THROMBOCYTOPENIC purpura following the use of the sulfonamides is a rare but serious complication. In some instances it appears to be the result of an acquired sensitivity to the drug, whereas in others it represents a true idiosyncrasy and may follow the initial experience with the sulfonamide. Werner<sup>1</sup> reported a case of thrombocytopenia which appeared after the administration of only 1 gram of sulfathiazole. This patient had a history of having received the same drug 20 days before without reaction. Toxic thrombocytopenia was described by Goldbloom et al<sup>2</sup> in a 50 year old female who had received only 6 grams of sulfapyridine. Hurd and Jacox<sup>3</sup> recently reviewed the literature on the subject of thrombocytopenia following the sulfonamides and added two more cases. When the platelet count of their sulfathiazole-sensitive patient had returned to normal, they retested him with sulfathiazole and sulfadiazine and noted the same type of toxic reaction with both drugs.

This report is not submitted merely to add another case history to the literature but rather to relate the therapeutic dilemma which developed when a sulfathiazole sensitive patient developed almost all of the known complications of scarlet fever.

### CASE REPORT

A white soldier, aged 19, was admitted to the Station Hospital on March 16, 1943, because of "a breaking out" on his body which he had first noted that morning. He had no other complaints and was anxious to return to duty. On physical examination the temperature, the pulse, and the respirations were normal. There was a widespread maculopapular rash on the face, neck, trunk, and extremities. The occipital and posterior cervical lymph nodes were enlarged. There were no Koplik spots visible in the mouth. A diagnosis of German measles was made and general supportive treatment was given. The rash gradually faded and the patient seemed perfectly well.

On the seventh hospital day, the temperature, which had been consistently normal, suddenly rose to 101° F, and a punctate erythematous rash became apparent on the patient's chest. At the same time, the patient began to complain of severe sore throat. The pharynx was acutely inflamed and the tonsils were covered partially by a grayish yellow exudate. Circumoral pallor was present and a typical strawberry tongue was seen. A diagnosis of scarlet fever was made and treatment was instituted. Because of the follicular tonsillitis, oral administration of sulfathiazole in divided doses was started. No history of previous sulfonamide therapy was obtained. After 19 grams had been given over a three day period, the drug was stopped.

\* Received for publication March 6, 1944

The day after the sulfathiazole was discontinued the patient began to bleed from his nose. This bleeding continued for four days. All conservative local and systemic measures were tried with but moderate success. The bleeding points were multiple, confined to the left nasal passage, and rapidly filled that cavity with a pulsating well of blood. However, the bleeding could be controlled with iced saline irrigations allowing adrenalin saturated packs to be inserted. Abnormal pulsation of the angular, temporal, and carotid arteries gave evidence of the vascular tension of the head and neck and partially explains why the tightly inserted nasal packs were gradually extruded by the pulsating blood clots.

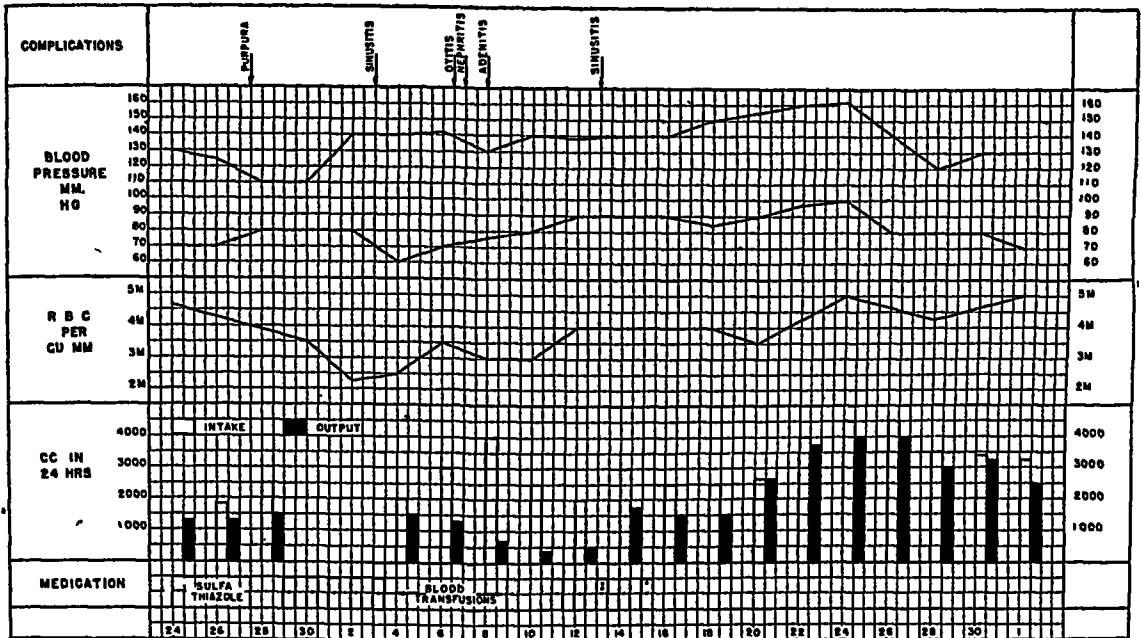


FIG 1

The second day of nasal bleeding a widespread petechial and ecchymotic rash appeared on the skin and mucous membranes. With continued hemorrhage the purpuric spots were seen on the gums, fauces, over the sacrum, about the elbows, and at other pressure points. At this time the red blood cell count was 2,630,000 per cu mm, the hemoglobin was 9.8 grams per 100 cc, the platelet count was 166,000 per cu mm and the white blood cell count was 25,350 per cu mm. The Rumpel-Leed test was positive. The urine was negative. The blood Kahn reaction was negative. In spite of four days of intensive treatment with small (250 cc) blood transfusions, vitamin K, vitamin C, and calcium subcarbonate, the hemorrhagic tendency increased as evidenced by the presence of blood in the urine and stools. A second platelet count done two days after the first, showed 100,000 platelets per cu mm. Although the bleeding time was longer than 15 minutes, the clotting time was normal.

After five days of persistent bleeding, the hemorrhagic tendency disappeared abruptly and the patient's general condition improved markedly. With the exception of the appearance of a purulent rhino-sinusitis, the next three days were uneventful. On the fourth day the patient's temperature became elevated and he complained of pain in his right ear. Conservative aural treatment was begun but on the following day a myringotomy under local anesthesia was performed because of increased pain and bulging of the drum. A hemolytic streptococcus was isolated from the aural discharge but the risk of further bleeding did not justify the use of chemotherapy.

Coincident with the development of the otitis media, a marked bilateral anterior and posterior cervical lymphadenitis was noted

The patient's course was further complicated by the development of the signs and symptoms of an acute glomerulonephritis. This was manifested by puffiness of the hands and face, diminished urinary output, marked pallor, elevated non-protein nitrogen and by the appearance of albumin, red blood cells, and casts in the urine. Coincident with the onset of all these complications the patient's condition became critical. For the next three days the pharyngeal airway became progressively decreased owing to the external pressure of the greatly enlarged cervical glands and the respiratory difficulty was further increased by a definite air hunger resulting from the marked anemia. Small blood transfusions and intravenous injections of 10 per cent glucose solution were given as supportive treatment with slow but progressive improvement. The dyspnea disappeared with the subsidence of the cervical adenitis, the urinary output increased, the edema cleared, and the aural and postnasal discharges diminished. However, with this general improvement, a definite hypertension developed which was accompanied by a persistently elevated sedimentation rate and albuminuria. The Mosenthal and phenolsulfonphthalein tests demonstrated impaired kidney function although the non-protein nitrogen was normal.

Within the next four weeks all signs of nephritis disappeared. The urine cleared completely, and the blood pressure, the sedimentation rate, the phenolsulfonphthalein and the Mosenthal tests were all within normal limits.

After one month of sick furlough, the patient returned to full military duty. A follow-up made six months later showed the patient to be in good physical condition.

#### COMMENT

Considerable variations occur in the enumeration of blood platelets owing to their tendency to clump and to certain other mechanical difficulties. Values below 200,000 per cu mm are generally considered to be less than average, whereas counts of less than 130,000 denote a pathological deficiency. The second platelet count of 100,000 per cu mm obtained in this case, together with the prolonged bleeding time, the normal clotting time and the poorly retracting clot were believed sufficient evidence to classify this purpura as one belonging in the thrombocytopenic group.

It has seemed feasible to us to assume that the thrombocytopenia was due to sulfathiazole. Whether the general toxicity of the hemolytic streptococcal infection was a significant additional factor in the causation of this condition cannot be positively stated. The Dicks<sup>4</sup> fail to mention thrombocytopenia as a complication of scarlet fever in their book, although there are a few reports in the literature of purpura following the malignant forms of smallpox, diphtheria, scarlet fever and other streptococcal infections.

Hemorrhage into the gastrointestinal tract and kidneys is a frequent finding in purpura. In some instances a true nephritis is simulated by the hematuria, albuminuria, and the depression of renal function. In the case presented the initial hematuria associated with the other hemorrhagic manifestations was thought to be an example of this pseudo-nephritis. The secondary hematuria occurring nine days later, after two negative urinalyses had been obtained, was considered to be a true post-scarlatinal nephritis.

Although it was desirable to retest this patient with sulfathiazole after his recovery, the severity of his reaction and the nearly fatal outcome did not justify this procedure.



## SUMMARY

A case of scarlet fever with thrombocytopenic purpura and severe hemorrhagic manifestations which developed following the administration of 19 grams of sulfathiazole by mouth during a three day period is reported. The extreme difficulty which was encountered in controlling the hemorrhagic manifestations is emphasized. The therapeutic impasse that was reached when, following the control of the hemorrhage, the patient developed suppurative otitis media, marked cervical lymphadenitis, severe sinusitis, and nephritis is mentioned. Multiple transfusions, local treatment and general supportive measures proved to be life saving in this instance.

The authors wish to express their indebtedness to Capt Harry Levitt, M C and to various members of the Surgical Service of the Station Hospital for their part in saving this soldier's life.

## BIBLIOGRAPHY

- 1 WERNER, W I Thrombocytopenic purpura following administration of sulfathiazole, Southwest Med, 1942, xxvi, 49
- 2 GOLDBLOOM, A A, GREENWALD, LOUIS, and REINSTEIN, HARRY Toxic reactions to sulfa-pyridine, Jr Lab and Clin Med, 1941, xxvii, 139
- 3 HURD, R W, and JACOX, R F Thrombopenic purpura developing as a complication of sulfathiazole and sulfadiazine therapy, Jr Am Med Assoc, 1943, cxxii, 296
- 4 DICK, G F, and DICK, G H Scarlet fever, 1938, The Year Book Publishers, Chicago, Illinois

## PROGRESSIVE (DISSEMINATED) COCCIDIOIDOMYCOSIS REPORT OF A CASE\*

By CHARLES D MARPLE, Capt, M C, A U S, *Santa Ana, California*

COCCIDIOIDOMYCOSIS, which is still occasionally and erroneously referred to as a "tropical disease," is an infection caused by the fungus *Coccidioides immitis* (Rixford and Gilchrist, 1896) and occurs endemically in the San Joaquin Valley of California and over large areas in the Southwest. The disease, both in its benign primary form and in the fortunately uncommon disseminated form, has become thoroughly familiar to military medical officers stationed in these areas during the present war. It is reasonable to believe that physicians in other regions of the United States will encounter occasional cases of coccidioidomycosis when men who have been stationed previously in the endemic areas return to their homes. For this reason even single case reports of disseminated coccidioidomycosis would seem worth publishing. This particular case is presented because of the rather complete observation of the clinical and laboratory course of the disease, because of the futile but somewhat suggestive treatment with coccidioidin vaccine and because of the unusual occurrence of paraplegia secondary to an extradural coccidioidal abscess.

The terms "progressive coccidioidomycosis" and "disseminated coccidioidomycosis" are synonymous with the older and less appropriate titles of "coc-

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From the Medical Department of the California State Prison, San Quentin, California

cidoidal granuloma" and "secondary, or chronic coccidioidomycosis" and are applied to the progressive, highly fatal form of the disease. The ratio of the incidence of this form of the disease to that of the frequently subclinical and ordinarily benign "primary coccidioidomycosis" is no greater than 1:500. For a discussion of nomenclature and for an excellent summary of our present knowledge of coccidioidomycosis, the reader is referred to the recent review by C. E. Smith.<sup>1</sup>

#### CASE REPORT

A 36 year old negro male entered the Charles Neumiller Hospital on April 15, 1941 because of "pain in the right foot" of one month's duration. His family history was not contributory. He denied any known contact with tuberculosis. He had been born in Texas and had lived there for 19 years. For five years he had been a porter on railroads operating between Los Angeles and Salt Lake City, and he had resided in Los Angeles between trips. From 1930 until 1937 he had served a prison sentence in the California State Prison at San Quentin. For nearly three years he had performed day labor on a ranch in Monterey County on the coast of California. From June 1940 until February 1941 he had lived in San Francisco. He denied ever having been a resident of the San Joaquin Valley.

The patient had had syphilis, first manifested by a chancre and positive blood serologic reaction in 1930 for which he had been treated with 15 injections of neoarsphenamine and 30 injections of a bismuth salt. Treatment had been discontinued after repeatedly negative blood and spinal fluid-serological tests had been obtained. In 1932 his spinal fluid had exhibited a negative Wassermann reaction, a normal protein content and a colloidal gold curve of 5544331000. There had been several unrelated accidents, operations, and minor illnesses. Review of the body by systems elicited no complaints prior to the onset of the presenting illness.

The present illness had begun with an attack of "the flu" about two months previously. This had consisted of chills and fever, generalized aches and pains, a moderately productive cough and a rapid and considerable weight loss over a short period of time. A fortnight later the patient had first noted the spontaneous occurrence of pain over the instep of the right foot. This pain had become progressively more severe and had radiated up the front of the lower leg. There was no history of trauma to the foot. At about the same time there had appeared on the bridge of his nose a painless erythematous swelling which had gradually increased in size. This swelling had been incised by a physician and had drained small amounts of pus persistently thereafter. A similar swelling had appeared on the radial side of the right forearm just above the wrist, had ruptured spontaneously and had exuded purulent material intermittently. Other swellings had appeared subsequently on both thighs, behind the left knee, on both upper arms, on the dorsum of the left hand and on the right side of the forehead. These swellings had grown in size and some had assumed a dusky red hue. There had been a weight loss in excess of 20 pounds in two months.

Physical examination revealed an emaciated negro male in no discomfort. Pupils were dilated and equal, the right pupil reacted to light, the left did not. There was a small subcutaneous abscess on the right side of the forehead. A similar but smaller abscess was present just above the inner canthus of the right eye. On the bridge of the nose was an erythematous swelling with a central eschar from which pus could be expressed. No abscesses were present on the neck or the trunk. Breath sounds were diminished at the right lung base posteriorly where dry râles could be heard. Cardiovascular examination was completely normal. No abdominal organs or masses could be felt. There were no enlarged lymph nodes. Reflexes were physiological and

equal throughout. There were several superficial abscesses on each thigh and one behind the left knee. There was a draining abscess above the right wrist and multiple fluctuant swellings on both upper arms. On the dorsum of the right foot was a tender, diffuse and slightly discolored swelling. There were numerous small and large traumatic scars on various portions of the body.

The results of the initial and subsequent laboratory studies are summarized in table 1. Skin tests with tuberculin (0.1 cc 1:10,000 dilution) and with coccidioidin

TABLE I  
Laboratory Record

| Date  | Blood     |       |        |    |    |            |          | Miscellaneous Laboratory Findings        |
|-------|-----------|-------|--------|----|----|------------|----------|--|
|       | RBC (mil) | Hgb % | WBC    | PN | LY | Eos / Baso | Sed Rate |  |
| 4/15  | 4 92      | 64    | 15,200 | 78 | 16 | 3/1        | 30       | Urine Pus cells 5-7/HPF, Alb Tr          |
| 19    |           |       |        |    |    |            |          | Blood Wa R and Kahn doubtful positive    |
| 23    |           |       |        |    |    |            |          | 5 sputa negative for tuberculosis        |
| 24    |           |       |        |    |    |            |          | <i>Cocc immutis</i> cultured from sputum |
| 28    |           |       |        |    |    |            |          | Spinal fluid globulin (-), 6 cells       |
| 29    | 4 22      | 64    | 11,750 | 75 | 33 | 1/0        | 31       | Spinal fluid Wa R and Kolmer pos ?       |
| 5/ 3  |           |       |        |    |    |            |          | Blood Wa R 2 plus, Kahn pos ?            |
| 8     | 4 55      | 75    | 18,500 | 68 | 28 | 4/0        |          | Urine albumin (-), 3 pus/HPF             |
| 9     | 4 56      | 69    | 11,400 | 70 | 26 | 2/0        | 30       |  |
| 10    | 4 70      | 69    | 12,400 | 69 | 26 | 3/0        |          |  |
| 11    | 4 78      | 64    | 14,100 | 69 | 18 | 3/7        |          |  |
| 12    | 4 77      | 64    | 12,200 | 69 | 19 | 4/4        |          |  |
| 13    | 4 47      | 64    | 18,850 | 77 | 11 | 1/9        |          | Urine albumin (-), 4-5 pus/HPF           |
| 26    | 4 35      | 69    | 13,600 | 76 | 23 | 1/0        | 10       |  |
| 6/ 7  | 5 72      | 69    | 16,250 | 52 | 39 | 5/4        | 28       | Spinal fluid Kolmer positive             |
| 24    | 5 08      | 69    | 14,450 | 83 | 17 |            | 1        |  |
| 30    |           |       |        |    |    |            |          | Urine albumin pos, 10 pus/HPF            |
| 7/ 8  | 4 95      | 69    | 16,200 | 76 | 22 | 1/0        | 2        |  |
| 17    | 5 12      | 69    | 21,600 | 86 | 10 |            | 32       | Urine albumin (-), 1-4 pus/HPF           |
| 21    | 4 23      | 61    | 25,400 | 90 | 8  |            | 32       |  |
| 28    | 3 35      | 52    | 20,750 | 88 | 11 |            |          |  |
| 8/ 5  | 3 96      | 58    |        |    |    |            |          |  |
| 7     | 5 40      | 68    | 20,100 |    |    |            |          |  |
| 11    | 3 94      | 64    | 14,750 | 77 | 19 |            | 32       |  |
| 14    | 4 82      | 69    | 13,400 | 76 | 22 |            | 24       |  |
| 18    | 4 74      | 69    | 18,400 | 78 | 18 | 1/2        | 25       |  |
| 22    | 3 79      | 64    | 20,800 | 76 | 20 | 2/1        | 28       |  |
| 31    | 4 10      | 69    | 18,800 | 85 | 13 | 1/0        | 23       |  |
| 9/ 6  | 4 36      | 64    | 19,100 | 90 | 9  | 1/0        | 27       |  |
| 15    | 4 32      | 64    | 18,350 | 81 | 19 |            | 27       |  |
| 22    | 4 36      | 69    | 30,300 | 89 | 11 |            | 28       | Blood Wa R (-)                           |
| 10/ 8 | 2 89      | 64    | 16,300 | 75 | 21 | 1/0        | 27       | Spinal fluid Culture neg                 |

(0.1 cc 1:1000 dilution) were strongly positive after 24 hours. Roentgenograms of the right foot revealed no pathological changes, but a chest plate showed an abscess cavity in the posterior portion of the left lower lobe. Pus was aspirated from several of the abscesses and cultured on Sabouraud's medium; the growth of *Coccidioides immitis* was confirmed by animal inoculation. One lesion was excised for pathological study. Cut section showed a central area of necrosis which was granular and slightly caseous, bounded by a narrow grayish zone. The histological report (Dr David A. Wood) stated "Section shows fatty and striated muscle tissue in which are large granulomatous areas and numerous abscesses. The granulomatous areas are characterized by broad zones of epithelioid cells and by centrally placed collections

of lymphocytes and necrotic debris. Spherules of *Coccidioides immitis* in various stages are present. Plasma cells and eosinophilic leukocytes are rather numerous."

The patient's course was generally downward although interrupted by a period of objective and subjective improvement during the time in which coccidioidin vaccine was administered. His temperature was persistently elevated, the daily maximum ranging from 99.6° F to 101.6° F (oral) except during the period of coccidioidin therapy when there were occasional elevations to as high as 104° F. During the first five weeks in the hospital there was rapid and progressive loss of weight and of strength. Treatment during this period consisted of supportive care, a vitamin barrage, supplemented by injections of liver extract, sedation and catharsis. On the thirty-ninth day of hospitalization he complained of "numbness and burning" of his feet and legs. At the same time he found it impossible to walk, owing partly to his general weakness, but also to the loss of proprioceptive sense in his lower limbs. The paresthesia and the loss of strength of the lower limbs extended upward progressively until, on the forty-eighth hospital day, urinary retention occurred. Control of the anal sphincter was lost one week later. Neurological examination at this time revealed the following significant findings: Bilateral absence of abdominal and Achilles tendon reflexes and marked weakness of the patellar reflexes, complete loss of superficial sensation over the feet and lower legs, inability to stand. The spinal fluid was clear and under no increase of pressure; microscopic examination and culture of the fluid were reported negative. On June 28, the seventy-fifth day of hospitalization, all reflexes below the costal margins were absent and sphincter control was completely lost.

A course of coccidioidin vaccine therapy was begun on May 23, the thirty-eighth day of hospitalization. Following preliminary skin and intramuscular tests for sensitivity injections of the vaccine were given intravenously on alternate days, beginning with a dose of 0.1 cc of a 1:1000 dilution and increasing the amount and strength given to a maximum dose of 2.0 cc of the undiluted vaccine. Twenty-three injections of undiluted vaccine in doses of 2.0 cc were given before the treatment was discontinued. Data concerning the dosage, the route of injection, and the reactions to individual injections are summarized in table 2. Whether because of the vaccine therapy, or because of a spontaneous remission in the course of the disease, during the first week in July there was a definite regression in the size of many of the subcutaneous abscesses. On July 14, for the first time in six weeks, the patient was able to void spontaneously and shortly thereafter his fecal incontinence became much less troublesome. Sphincter control was again lost after approximately four weeks and the patient was incontinent for the remainder of his illness.

During the entire period of hospitalization the patient suffered severe anorexia, persistent insomnia and frequent spells of "twitching and jumping" of the legs. There was a progressive weight loss and a mild degree of anemia for which three transfusions were given during the month of July. It became obvious that he was losing ground during the last week in August and his final days were characterized by a semicomatose state. He died on the one hundred and eighty-fifth day of hospitalization.

**Autopsy** (October 23, 1941). The body was that of a well-developed, but extremely emaciated negro male of about 40 years. There was a small subcutaneous thickening on the right side of the forehead. There was a small eschar from which pus could be expelled on the bridge of the nose. Over the thyroid cartilage was a sinus opening into the subcutaneous tissues. There were no enlarged palpable lymph glands. There were large and deep decubitus ulcers over the sacrum, over the right sacroiliac joint and over both greater trochanters. Similar ulcers were present over both external malleoli. There was a large subcutaneous abscess on the dorsum of the right foot. **Thorax.** Beneath the xiphoid process was a small abscess. There were extrapleural abscesses beneath the seventh and eighth ribs anteriorly on the

TABLE II  
Coccidioides Vaccine Therapy

| Dates | Vol<br>c c | Dilu-<br>tion | Route<br>of Inj | Reactions  |
|-------|------------|---------------|-----------------|--|
| 5/23  | 0 1        | 1 1000        | I M             | No constitutional reaction Slight local tenderness       |
| 5/26  | 0 1        | 1 1000        | I V             | No local or systemic reaction                            |
| 5/28  | 0 2        | 1 1000        | I V             | Transient pains up arm and into chest after injection    |
| 5/30  | 0 4        | 1 1000        | I V             | No reaction  |
| 6/ 1  | 0 8        | 1 1000        | I V             | No reaction  |
| 6/ 3  | 0 1        | 1 100         | I V             | No reaction  |
| 6/ 5  | 0 2        | 1 100         | I V             | No reaction  |
| 6/ 6  | 0 4        | 1 100         | I V             | No reaction  |
| 6/ 7  | 0 8        | 1 100         | I V             | Noted unusual taste in mouth immediately after injection |
| 6/ 8  | 1 0        | 1 100         | I V             | Noted taste again Stated that he can use legs better     |
| 6/ 9  | 0 1        | 1 10          | I V             | Noted taste again No constitutional reaction             |
| 6/11  | 0 2        | 1 10          | I V             | No reaction  |
| 6/13  | 0 4        | 1 10          | I V             | Taste in mouth No other reaction                         |
| 6/15  | 0 8        | 1 10          | I V             | No reaction other than taste in mouth                    |
| 6/16  | 1 0        | 1 10          | I V             | Temperature to 102 6° F following injection              |
| 6/17  | 0 1        | 1 1           | I V             | No reaction  |
| 6/19  | 0 2        | 1 1           | I V             | No reaction  |
| 6/21  | 0 4        | 1 1           | I V             | No reaction  |
| 6/23  | 0 8        | 1 1           | I V             | No reaction  |
| 6/25  | 1 0        | 1 1           | I V             | Temperature to 102 6° F Temperature to 104 2 on 6/26     |
| 6/27  | 1 0        | 1 1           | I V             | Temperature to 103 4° F                                  |
| 6/29  | 1 0        | 1 1           | I V             | Vomited 20 minutes after injection                       |
| 7/ 1  | 1 0        | 1 1           | I V             | No reaction  |
| 7/ 3  | 1 0        | 1 1           | I V             | Temperature to 104 0° F following injection              |
| 7/ 5  | 1 0        | 1 1           | I V             | No reaction  |
| 7/ 7  | 1 0        | 1 1           | I V             | No reaction  |
| 7/ 9  | 1 0        | 1 1           | I V             | "Knees burn " No fever or systemic reaction              |
| 7/11  | 1 0        | 1 1           | I V             | No reaction  |
| 7/13  | 1 0        | 1 1           | I V             | No reaction  |
| 7/15  | 1 0        | 1 1           | I V             | Nauseated and vomited afternoon following injection      |
| 7/17  | 1 0        | 1 1           | I V             | Cold chill following injection temperature to 104 2° F   |
| 7/19  | 1 0        | 1 1           | I V             | Cold chill following injection temperature to 101 6° F   |
| 7/21  | 1 0        | 1 1           | I V             | No reaction  |
| 7/23  | 2 0        | 1 1           | I V             | Temperature to 103 4° F following injection              |
| 7/25  | 2 0        | 1 1           | I V             | No reaction  |
| 7/27  | 2 0        | 1 1           | I V             | No reaction  |
| 7/29  | 2 0        | 1 1           | I V             | No reaction  |
| 7/31  | 2 0        | 1 1           | I V             | Temperature to 103 0° F in afternoon                     |
| 8/ 2  | 2 0        | 1 1           | I V             | Temperature to 100 4° F following injection              |
| 8/ 4  | 2 0        | 1 1           | I V             | No reaction  |
| 8/ 6  | 2 0        | 1 1           | I V             | Temperature to 101 4° F in afternoon                     |
| 8/ 8  | 2 0        | 1 1           | I V             | No reaction  |
| 8/10  | 2 0        | 1 1           | I V             | No reaction  |
| 8/12  | 2 0        | 1 1           | I V             | No reaction  |
| 8/14  | 2 0        | 1 1           | I V             | No reaction  |
| 8/16  | 2 0        | 1 1           | I V             | No reaction  |
| 8/18  | 2 0        | 1 1           | I V             | Legs burn Temperature to 100 4° F after injection        |
| 8/20  | 2 0        | 1 1           | I V             | No reaction  |
| 8/22  | 2 0        | 1 1           | I V             | No reaction  |
| 8/24  | 2 0        | 1 1           | I V             | Complains of "jumping in the legs "                      |
| 8/26  | 2 0        | 1 1           | I V             | Complains of "jumping in the legs "                      |
| 8/28  | 2 0        | 1 1           | I V             | No reaction  |
| 8/30  | 2 0        | 1 1           | I V             | No reaction  |
| 9/ 1  | 2 0        | 1 1           | I V             | No reaction  |
| 9/ 3  | 2 0        | 1 1           | I V             | No reaction  |
| 9/ 5  | 2 0        | 1 1           | I V             | No reaction  |

right side and above the ninth rib on the left side of the thoracic cage. Both lungs were free except for a few strands of adhesions at the right base. The left pleural cavity contained half an ounce of amber fluid, the right pleural cavity, four ounces of similar fluid. On the right side of the chest posteriorly were four extrapleural abscesses, one at the inferior angle of the pleural cavity, the others adjacent to the eighth and ninth vertebral bodies. Exploration of these cavities with a probe revealed extensive destruction of the vertebral bodies and communication with the spinal canal. No opening could be found into the subarachnoid space and there was no evidence of communication with this space. There were no intrapleural abscesses. The lungs were grossly congested, no nodules or abscess cavities could be seen or felt. Pus was obtained from a moderately enlarged paratracheal lymph node. The heart was small and the valves were essentially normal. Abdomen. A half dozen pinhead sized abscesses were present on the anterior surface of the liver. The spleen, the stomach and the intestines were grossly normal. The kidneys were normal in size, but their surfaces were somewhat finely nodular. There were no nodules nor abscesses in the pelvis.

Organs (Dr Alvin Cox) The left lung weighed 680 grams. Its pleural surfaces were smooth. Palpation of the lung revealed no nodules and the cut surface appeared normal except for moderate hyperemia and partial collapse posteriorly. One peribronchial lymph node contained a sharply defined cavity filled with white pasty material. A second, smaller lymph node was almost completely replaced by pale brown caseous material. The right lung weighed 780 grams and was similar to the left except for a subapical nodule 3 mm in diameter with a central white opaque area and a peripheral gray remnant. In the periphery of the lower lobe was a less well-defined consolidated area 2 cm broad. Nearby were indistinct gray nodules about 1 mm in diameter. The bronchi and the pulmonary arteries showed no abnormalities. The spleen weighed 130 grams. The capsule was wrinkled and the pulp was normal except for a dozen sharply defined, calcified nodules up to 5 mm in diameter. The liver weighed 2020 grams. The cut surface was normal. The portal vein branches were normal. The gall-bladder was normal. The kidneys together weighed 300 grams. The capsules stripped easily revealing mottled pale gray and dark red surfaces which were irregularly nodular. Clusters of pale yellow nodules protruded slightly and there were poorly defined pitted areas. The cut surfaces showed irregular gray streaks and spots, particularly in the cortices from whence some extended into the medullae. The pelvis and ureters were thickened in spots.

Microscopic (Dr Alvin Cox) Lungs In the upper portion of the right lung just beneath the pleura was a large mass of acellular material about twice the area of a low power field surrounded by a dense fibrous capsule. This contained a moderate amount of black pigment in small clumps and scattered lymphocytes. Toward the inner surface were several multinucleated giant cells and fibrous tissue containing spherules of *Coccidioides immitis*. In other sections the lung lesions were more recent, composed of irregular areas of consolidation with an exudate of macrophages laden with brown pigment, lymphocytes and polymorphonuclear leukocytes. Elsewhere were areas of caseation with peripheral tubercle formation and early fibrosis. Here also were giant cells and spherules. No endosporulating forms were seen, but the organisms were otherwise characteristic of *Coccidioides* spherules. Peribronchial Lymph Nodes Large caseous areas were bordered by a wall of dense fibrous tissue and giant cells, and spherules were present near the junction of tissue and caseous material. One spherule contained endospores. Satellite fibrous tubercles were present. Liver Normal except for nodules described grossly. These had dense fibrous walls containing a few lymphocytes and centers composed of granular material which was extensively calcified. No spherules and no satellite lesions were found. Spleen Two nodules one half centimeter in diameter had a structure similar

to the nodules in the liver No spherules were seen Kidneys In large areas there were markedly irregular infiltrations of the cortical parenchyma by lymphocytes and polymorphonuclear leukocytes with scattered eosinophiles and macrophages The tubules in the cortex were hardly visible in many places because of extensive collapse and atrophy a few tubules were dilated and contained pus The glomeruli were less altered and many appeared normal There was a diffuse increase in interstitial tissue throughout This was most marked in the medulla where cellular infiltration was slight No *Coccidioides* spherules were seen Other parts of the kidneys showed an essentially normal structure

*Pathological Discussion* The lesion in the upper part of the right lung had the appearance of a primary focus whereas the other granulomatous lesions in the lung were more recent and progressive The lymph node lesions were like the old lung lesion, although, if they were part of a primary complex, it is difficult to explain their presence on the side opposite to that of the lung lesion and their absence on the same side However, there may have been other involved mediastinal nodes and it is possible that retrograde spread along lymphatic pathways occurred from these The nodules in the liver and in the spleen had a different appearance and were, presumably, not caused by the fungus They did not resemble syphilitic lesions The presence of one small lesion in a splenic vein branch suggested that some or all of these calcified nodules may have been phleboliths The pyelonephritis was independent of the coccidioidal granuloma and was probably an important cause of death

## DISCUSSION

A considerable number of the common features of disseminated coccidioidomycosis are demonstrated by this case Dark skinned races exhibit a greater tendency to develop the disseminated form of the disease than does the white race The disease is acquired by inhalation of the fungus (chlamydospores) and the transmission of coccidioidomycosis from man to man is unknown The patient had always lived in the proximity of known endemic areas and he had frequently traveled through these areas The attack of "flu" which preceded the appearance of the subcutaneous abscesses was undoubtedly a manifestation of coccidioidomycosis, but it is somewhat doubtful that it represents a primary infection as the patient had been an inmate of a city prison in a non-endemic area for some weeks previously However, in the usual case, dissemination generally follows shortly after the infection has been acquired

The terminal illness was characteristic of disseminated coccidioidomycosis There was the typically slow progression downward punctuated by periods of relative remission The course was febrile throughout Severe anorexia was accompanied by progressive weight loss and terminal cachexia Multiple decubitus ulcers developed during the last month Despite the liberal use of vitamins, liver extract and various iron preparations there was a persistent anemia which responded only temporarily to blood transfusions The organs whose involvement gave rise to clinical symptoms were those commonly involved during dissemination by the fungus, namely, the lungs, the integument and the skeletal system, including both the bones and the muscles

The paraplegia was undoubtedly the result of pressure on the spinal cord by the abscesses which eroded through the vertebral bodies from the extrapleural space into the extradural space There was no evidence that the patient's syphilis played any rôle in the neurological symptoms It is unfortunate that permission to open the cranial vault and the spinal canal was not obtained, but

TABLE III  
Complement Fixation and Precipitin Tests for *Coccidioides immitis* on Serum in the Case Here Reported

| Dates   | Complement Fixation Tests<br>(serial dilutions of 25 cc of serum) |     |     |      |      |      |       |       | Precipitin Tests<br>(serial dilutions of antigen) |      |       |  | Remarks  |    |
|---------|---|-----|-----|------|------|------|-------|-------|---|------|-------|--|--|----|
|         | 1 2   | 1 4 | 1 8 | 1 16 | 1 32 | 1 64 | 1 128 | Undil | 1 10  | 1 40 | 1 100 |  |  |    |
| 5/15/41 | ++  | ++  | ++  | ++   | ++   | 0    | 0     | ++    | ++  | 0    | 0     | Strong complement fixation with definite but lower precipitin titer, characteristic of disseminated coccidioidomycosis |  |    |
| 5/20/41 | ++  | ++  | ++  | ++   | ++   | 0    | 0     | ++    | ++  | ++   | +     |  | No significant change in titer of complement fixation but a definite rise in precipitins<br>No significant change<br>No significant change |    |
| 6/10/41 | ++  | ++  | ++  | ++   | ++   | ++   | 0     |       | ++  | ++   | ++    |  |  | ++ |
| 7/10/41 | ++  | ++  | ++  | ++   | ++   | ++   | 0     |       | ++  | ++   | ++    |  |  | ++ |
| 7/29/41 | ++  | ++  | ++  | ++   | ++   | ++   | 0     |       | ++  | ++   | ++    | ++   |  |    |
| 8/16/41 | ++  | ++  | ++  | ++   | ++   | ++   | 0     | ++    | ++  | ++   | ++    |  |  |    |
| 9/ 2/41 | ++  | ++  | ++  | ++   | ++   | ++   | 0     | ++    | ++  | ++   | ++    |  |  |    |



sterile cultures of spinal fluid removed four days before death minimize the possibility of intrathecal involvement. In about 25 per cent of the cases of disseminated coccidioidal infection there is involvement of the central nervous system.<sup>2</sup>

Various observers have treated coccidioidal infections with vaccines consisting of ball-mill grinds of the fungus. Results have been equivocal with Jacobson<sup>3</sup> reporting the most consistently favorable results. Such a vaccine was tried on this patient with the utmost skepticism and the dosage and the intervals of treatment were limited to those previously reported in the literature. It is recognized that the subjective and objective improvement which accompanied the use of the vaccine may have represented an ordinary remission in the course of the disease. However, the degree to which the subcutaneous lesions diminished and the relief of neurological symptoms, indicating a similar recession of the abscess pressing upon the spinal cord, demonstrated a degree of regression which is not noted frequently in this disease. Even more impressive than these objective changes were the subjective improvement during this period of treatment with vaccine, the improvement in appetite, the regaining of strength and the boost in the patient's morale. It would seem that, in the absence of any effective chemotherapeutic agent, a trial of vaccine would be indicated in any case of disseminated coccidioidomycosis. Furthermore, there is no evident contraindication to the use of greater doses of vaccine than have hitherto been reported.

The clinical course of disseminated coccidioidomycosis is ordinarily indistinguishable from that of disseminated tuberculosis, or of other mycoses. The diagnosis is established by the recovery of *Coccidioides immitis* from specimens of sputum or pus, or the demonstration of the typical *Coccidioides* spherules in tissue sections. Identification of the fungus depends upon the demonstration of its diphasic character by culture and animal inoculation with the recovery of spherules from a guinea pig or mouse. Sabouraud's medium or the special medium developed at Stanford University<sup>1</sup> are particularly useful for the cultivation of *Coccidioides immitis*. Either guinea pigs or mice can be used for animal inoculation, intraperitoneal or subcutaneous injection of material is satisfactory. The coccidioidin skin test, analogous to the tuberculin intradermal test, is useful for screening patients, although its specificity has been questioned recently. Emmons<sup>4</sup> has shown that a cross-sensitivity exists with the fungus, *Haplosporangium parvum*. Complement fixation and precipitin tests are valuable for following the course of the disease. Both tests are almost always positive in severe infections. Although the precipitins are poorly demonstrable in most disseminated infections, the titer of the complement fixation ordinarily rises parallel to the severity of the infection. In the case presented all laboratory aids were utilized and all were positive for the disease. The results of repeated precipitin and complement fixation tests performed on the patient are summarized in table 3.

#### SUMMARY

1 A case of disseminated coccidioidomycosis with fatal termination is presented.

2 Points of particular interest are (a) the paraplegia resulting from pressure of an extradural abscess on the spinal cord, (b) the rather complete clinical and laboratory observations, and (c) the trial of coccidioidin vaccine therapy.

3 In the absence of any useful chemotherapeutic agent, the further trial of coccidioidin therapy in the disseminated disease is suggested

The author expresses his appreciation to Dr Leo L Stanley, Chief Surgeon (on leave of absence), California State Prison, San Quentin, and to Drs Charles E Smith, Alvin Cox and David A Wood of the Stanford University School of Medicine for their assistance in the study of this patient

#### BIBLIOGRAPHY

- 1 SMITH, C E Coccidioidomycosis, *Med Clin N Am*, 1943, xxvii, 790 .
- 2 COURVILLE, C B, and ABBOTT, K H Pathology of coccidioid granuloma of the central nervous system and its envelopes, *Bull Los Angeles Neurol Soc*, 1938, iii, 27-41
- 3 JACOBSON, H P Immunotherapy for coccidioid granuloma, report of cases, *Arch Dermat and Syph*, 1939, xl, 521-540
- 4 EMMONS, C W, and ASHBURN, L L The isolation of *Haplosporangium parvum* n sp and *Coccidioides immitis* from wild rodents Their relationship to coccidioidomycosis, *Pub Health Rep*, 1942, lvii, 1715

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#### FAMILIAL MYASTHENIA GRAVIS \*

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THE etiology of myasthenia gravis is still a much debated question The influence of heredity on the disease has not been accepted by the great majority of observers Authorities like Ford,<sup>1</sup> Cruschman,<sup>2</sup> McCarthy,<sup>3</sup> Wilson,<sup>4</sup> Wechsler,<sup>5</sup> Campbell and Bramwell<sup>6</sup> have rejected it and Viets<sup>7</sup> hesitated to pass an opinion However, Keschner and Strauss<sup>8</sup> suggest a congenital disposition to the disease, and Bing,<sup>9</sup> Riley and Frocht,<sup>10</sup> Marinesco,<sup>11</sup> Hart,<sup>12</sup> and Rothbart,<sup>13</sup> each reporting cases of familial myasthenia gravis, believe in some hereditary influence

Since the only way to prove or disprove each theory is to add more case reports to the few on record, without entering into the question, I should like to add to the others one more instance of familial myasthenia gravis

#### CASE REPORTS

*Case 1* A T was a 38 year old woman, born in the United States of Albanian parentage, married, with three children Her father died of cerebral hemorrhage at 67, her mother died of complications from an abdominal operation at 40, two brothers and one sister were living and well, another sister was affected by the same disease The patient had had measles and whooping cough as a child but had been otherwise healthy She married at 20 and went through two normal pregnancies

Ten years before admission she went to work in a radio factory and was employed in a room in which the temperature was kept at an exceedingly high level She attributed the onset of her disease to this cause After being employed there for six or seven months she gradually became weaker and weaker, being completely exhausted at night She gave up her job but her symptoms did not improve The eyelids began to droop, she noticed a slight strabismus and was so weak especially during her menstrual periods, that she became almost helpless

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With the event of her third pregnancy she made a marked improvement, and gave birth at term to a healthy child. A few weeks after delivery, however, all of her symptoms returned more aggravated than before. She could barely talk or swallow, the slightest effort exhausted her, the limbs became cold and heavy, and she was practically helpless.

On physical examination the patient was quite obese. Color and expression were fair. There was a marked drooping of the eyelids and a pronounced strabismus. The thyroid was slightly enlarged. Pulse was 85 and of good quality. Blood pressure was 120 mm Hg systolic and 70 mm diastolic. The heart and lungs were normal. The abdomen was soft. The muscles were flabby and the ordinary reflexes normal. Blood count was normal, blood chemistry normal, Wassermann reaction negative, urinalysis normal. The basal metabolic rate was  $-10$ . Radiography was negative for mediastinal tumor or other signs of enlarged thymus.

The patient was put on prostigmine bromide tablets with a slight improvement. The medication was changed to prostigmine methylsulphate hypodermically with a spectacular amelioration of all symptoms. Using two ampules a day for two weeks, she became stronger each day. The dose was gradually reduced until she was again put on prostigmine bromide tablets. At the time of this report she was almost well and was using the medicine only during menstrual periods or when an occasional symptom reappeared.

*Case 2* Rose S., sister of the preceding, was 28, single. She had had measles and pneumonia as a child, and a tonsillectomy when nine years old. She had been healthy and normal up to the age of 18, when she went to work with her sister in the same factory and under the same conditions. She also attributed her disease to the work.

The symptoms in her case were more rapid and more severe. She became bed-ridden with marked ptosis, severe dysphagia, difficulty in speaking and using her limbs. During an attack of head cold she almost choked trying to cough up some mucus. Often she could hardly breathe.

Physical examination showed no abnormalities except the ptosis and the extreme flabbiness of the muscles of the limbs. The only abnormal laboratory finding was an occasional slight excess of creatinine. Roentgen-rays of the chest were negative.

This sister was put on prostigmine methylsulphate, hypodermically administered, with moderate results immediately. The addition of ephedrine and potassium salts did not help much. There were slight remissions when she was able to get along with the tablets of prostigmine bromide, but usually she had to revert to the ampules, requiring occasionally some atropine to relieve the increased peristalsis.

## SUMMARY

Myasthenia gravis in two sisters is reported. Prostigmine was very effective in one but not in the other. Inasmuch as we know that remissions are common in the disease, the improvement of the first sister may be due to prostigmine or to the natural course of the disease. Both sisters noticed their symptoms for the first time after working in a greatly overheated room. Even if this is a coincidence, it is a very unusual one and should be reported.

## BIBLIOGRAPHY

- 1 FORD, F. R. Diseases of the nervous system in infancy, childhood and adolescence, 1937, Charles C. Thomas, Baltimore, page 889.
- 2 CRUSCHMAN, H. Handbuch der Neurologie, 1936, Springer, Berlin, vol. 16, pages 1005-1022.

- 3 MCCARTHY, D J Osler's Modern Medicine, 3rd Ed, 1928, Lea and Febiger, Philadelphia, vol 6, pages 803-820
- 4 WILSON, S A K Neurology, Ed by A Miriam Bruce, Vol 1-2, E Arnold and Co, Bruce Publ Co, St. Paul, Minn
- 5 WECHSLER, I Textbook of clinical neurology, 1939, W B Saunders, Philadelphia, page 202
- 6 CAMPBELL, H, and BRAMWELL, E Myasthenia gravis, Brain, 1900, xxiii, 277-336
- 7 VIETS, H R Present status of myasthenia gravis, Arch Neurol and Psychiat, 1942, xlvii, 859-862
- 8 KESCHNER, M, and STRAUSS, I Arch Neurol and Psychiat, 1921, xlvii, 337
- 9 BING, R Textbook of nervous diseases, 1939, C V Mosby and Co, St Louis, pages 181-185
- 10 RILEY, H A, and FROCHT, M Familial occurrence of myasthenia gravis, Arch Neur and Psychiat, 1943, xlix, 904-908
- 11 MARINESCO, G New contribution to pathogenesis of myasthenia, Bull et mem Soc med d hôp d Paris, 1925, xliii, 1369
- 12 HART, H H Myasthenia gravis with ophthalmoplegia and constitutional anomalies in sisters, Arch Neur and Psychiat, 1927, xviii, 439-442
- 13 ROTHBART, H B, JR Myasthenia gravis in children, Jr Am Med Assoc, 1937, lviii, 715-717

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## ACUTE LUPUS ERYTHEMATOSUS DISSEMINATUS A REPORT OF A CASE IN A MALE WITH ASSOCIATED ATYPICAL VERRUCOUS ENDOCARDITIS (LIBMAN-SACKS)\*

By S GILBERT BLOUNT, JR, M D, and JOHN T BARRETT, 1st Lt, M C, A U S

THE present concept of the symptom-complex known as acute lupus erythematosus disseminatus has been formulated over the period of the last 100 years.

Hebra,<sup>1</sup> in 1845, first described lupus erythematosus as a local cutaneous lesion under the name "seborrhea congestiva." Six years later Cazenave<sup>2</sup> gave the disease its present name. It was not until 1872 that Kaposi<sup>3</sup> subdivided the disease into "lupus erythematosus discoides" and "lupus erythematosus discretus and aggregatus." He was the first to realize the generalized and systemic manifestations of the latter form with its attending grave prognosis, as three of his 11 cases died while under observation. The clinical picture as we know it today was, in general, adequately described by this early investigator.

Sir William Osler,<sup>4</sup> in 1895, published the first of three series of cases under the heading "On the Visceral Manifestations of the Erythema Group of Skin Diseases," the other series being reported in 1900<sup>5</sup> and in 1904<sup>6</sup>. It was Osler who initiated the modern investigation of this syndrome, in particular, as regards the visceral and general systemic nature of the condition.

In 1924 Libman and Sacks<sup>7</sup> first recognized and described a "hitherto undescribed form of valvular and mural endocarditis" or "atypical verrucous endocarditis."

Since 1924 this clinico-pathologic entity has been widely and thoroughly studied both from the clinical and the pathological standpoints with considerable lack of unanimity of opinion as to its clinical manifestations or the pathological

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findings Klemperer, Pollack, and Baehr,<sup>8</sup> however, in 1941, presented a thorough study of both the gross and histological pathology of the disease that provides a firm pathologic foundation

#### CASE REPORT

G T, an American schoolboy of Italian parentage, was first admitted to the Rhode Island Hospital on July 14, 1943, at the age of 15, complaining of fever of two weeks' duration

*Present Illness* Seven months before admission the patient experienced painful swelling of the right ankle which prevented walking. This cleared up within a few days and the patient was symptom free until four weeks before entry. At that time his right knee became swollen and painful, however, this disappeared within a week under home treatment.

Beginning 14 days before admission there was a gradual onset of fever which was continuous in nature and reached its height during the late afternoon. During this period his appetite waned and he felt nauseated on several occasions, but there was no actual vomiting. Bowel habits were unusual in that the patient had from one to three stools a day, not accompanied by abdominal cramps. The stools at no time contained blood or mucus. For the week preceding entry the patient complained of pain in his ribs, particularly at the right costal margin. This pain was accentuated by deep breathing. For two or three days prior to admission the patient developed a hacking, non-productive cough. A history of a 20-pound weight loss in the two months preceding admission was obtained. He consulted two different doctors, and was given some large white pills which he was told were "good for infection." The patient took two of these pills every four hours for the four days before entry. There was no apparent effect on the elevated temperature and the patient was referred to the hospital.

*Past History* The patient stated that he had been healthy most of his life. There were no acute infections or diseases since early childhood. He had had the usual childhood exanthemata, but gave no history of rheumatic fever, chorea, scarlet fever or diphtheria. He underwent a tonsillectomy at the age of seven because he was sickly and was having frequent colds. This was followed by subjective improvement. Seven months before admission the patient had an "infection" of the middle and index fingers of the right hand which required a month to heal without specific treatment.

*Family History* The father had tuberculosis and had undergone a three-stage thoracoplasty in a local sanatorium. He was discharged from the sanatorium one and one-half months before the patient's entry. There was no history of other disease or allergic manifestations.

*Review of the Systems* A careful review of the systems elicited nothing of significance.

*Physical Examination* Pulse 120. Respirations 30. Temperature 104.8° F. Blood pressure 110 mm Hg systolic and 30 mm diastolic.

The patient appeared to be large for his age and showed signs of obvious weight loss. He lay flat in bed in no distress. No jaundice or cyanosis was present. The face appeared flushed and the skin over the V of the neck and over the wrists revealed small, pigmented, plaque-like areas.

*Head* There were no scars, deformities, or mastoid tenderness.

*Eyes* Pupils were round, regular, and equal, reacting to light and accommodation. There was no nystagmus. There was slight scleral injection. Examination of the fundi revealed nothing remarkable.

*Ears* There was no discharge or redness. The tympanic membranes were not unusual.

*Nose* There was no discharge or obstruction The septum was intact

*Mouth* The teeth were in fair repair The tongue was heavily coated The papillae were enlarged

*Pharynx* Considerably reddened, particularly in the area of the tonsils and the anterior pillars

*Neck* There was no stiffness There was moderate enlargement of the lymph nodes in both anterior and posterior cervical chains The trachea was in the midline without tug The thyroid was not palpable

*Spine* There were no structural deformities There was slight costo-vertebral angle tenderness on the left

*Thorax* There were no structural deformities Expansion was full and equal with respiration

*Lungs* Clear to auscultation and percussion There were no râles

*Heart* Heart was not enlarged to percussion and apical impulse was felt at the nipple line No thrill or shock was detected Sounds were of good quality There was a systolic murmur heard at the apex and in the aortic region, which was not transmitted No diastolic murmur was detected  $P_2$  was greater than  $A_2$   $M_2$  was greater than  $M_1$  Rate was rapid and rhythm regular

*Abdomen* Soft, no spasm or tenderness Liver, spleen, and kidneys were not palpable No masses were felt

*Genitalia* Normal adult male

*Rectal* Rectal sphincter tone was good Prostate was not enlarged There was no blood on the examining finger

*Reflexes* Rather sluggish, but equal throughout

*Extremities* There were no swollen, tender or warm joints There was no edema Fingers were slightly suggestive of a fusiform shape No subcutaneous nodules were felt

*Course* During the first week the patient remained a diagnostic problem The temperature was suggestive of a septic infection, spiking daily to about 103° F and never below 100.5° F The pulse increased proportionately, running between 100 and 110 The laboratory examinations revealed some interesting findings a persistently low white cell count, a marked anemia, and a negative blood culture

On the seventh hospital day a peculiar rash developed over the bridge of the nose and cheeks, butterfly-like in design It was at this time that the diagnosis of acute lupus erythematosus disseminatus was first suggested

Examination of the fundi now revealed blurring of the disc margins with elevation of about 1½ diopters This was present in both fundi and was interpreted as bilateral papilledema

During the next week there developed a stomatitis and beginning ulceration of the posterior wall of the pharynx He perspired profusely during the morning hours and complained rather bitterly about a sore throat Although his general condition was becoming weaker, he voiced no other complaints On the fourteenth hospital day he was tested with Old Tuberculin 1:10,000, which was read as negative On the eighteenth day the patient had an acute episode consisting of chills and fever to 105.4° F The skin lesions on the face, hands, and neck became more pronounced Respirations and pulse rate were increased and the patient appeared extremely sick

Examination of the lungs revealed them to be clear to auscultation and percussion The cardiac murmur detected on admission was still present and there was noted for the first time a gallop rhythm which persisted until death That night the patient had a nose bleed which was stopped with some difficulty During this time the anemia became more marked, and a platelet count was reported as 100,000 per cu mm Two electrocardiograms were reported as showing changes indicative of an acute process and not inconsistent with the diagnosis of pericarditis

The only treatment during this time was of a supportive nature, consisting of a diet high in carbohydrate and vitamin content with added parenteral vitamins. Several blood transfusions were given and pentnucleotide was started with the idea of combating the leukopenia. During this period the urine was not remarkable, showing only a trace of albumin, a specific gravity ranging from 1.010 to 1.020 with only a rare red blood cell and 2 to 100 white blood cells per H P F in centrifuged specimens.

On the twelfth hospital day sulfadiazine, 1 gram every four hours, was started on an empirical basis. However, it was soon found to be ineffective and was stopped on the eighteenth day. At that time the patient became mentally cloudy and disoriented and this condition persisted, more or less, until death. Up until that time the patient had been taking fluids well, but then, with few exceptions, fluids and diet had to be forced.

On the twenty-second day he complained of difficulty in breathing and shortly afterwards coughed up a large clot of blood, after which he felt better. Respirations dropped from 36 to 24. On the same day the nurse reported rectal bleeding. It seemed as though a generalized bleeding tendency was present. During that week the temperature ranged daily from normal to 103.5° F, the spike usually occurring about 7 a.m.

The last week of the patient's life was one of a rapid and progressively downward course. The anemia became very marked despite transfusions. The red blood cell count fell to 870,000 per cu mm and the hemoglobin to 2.5 grams per 100 cc of blood (Sheard-Sanford). The white blood cell count dropped to 2,000 per cu mm with 65 per cent polymorphonuclear leukocytes, and 33 per cent lymphocytes. He became very restless and uncooperative. There was a marked ulceration about the anterior pillars and in the tonsillar regions, with ulceration and soreness of the mouth. Bleeding of the nose and mouth was observed on several occasions. On the twenty-sixth day the patient was very drowsy, complained of difficulty in breathing and pain in the abdomen.

On the day before death the patient stated that he felt fine and he looked better than he had during the preceding 10 days. Examination of his heart on this day revealed a gallop rhythm and sounds definitely suggestive of severe myocardial damage. There was slight dullness to percussion at both lung bases with breath sounds diminished over these areas. No definite râles were heard. The temperature continued to spike during the last week with the patient perspiring profusely.

On the day of death the temperature rose to 106° F for a 24 hour period. On the evening of the thirty-second hospital day, 10 minutes after the cessation of a blood transfusion, respirations became labored, the pulse weakened, and the blood pressure fell to 80 mm Hg systolic and 50 mm diastolic. The patient was confused, cold and sweating. He was given oxygen and Eschatin intravenously. The general condition became somewhat better, however, he rapidly grew worse and died at 7:00 p.m.

During the entire hospital stay the urine output remained adequate, the patient voiding over 1500 cc of urine a day. Five blood cultures were reported as negative with one blood culture, taken on the day of death, reported as containing very many colonies of *Staphylococcus aureus*, coagulase positive. On that day the blood examinations showed the hemoglobin to be 2.3 grams per 100 cc of blood with 1,000 white blood cells, of which only 1 per cent was polymorphonuclear leukocytes and 99 per cent were lymphocytes.

**Urinalysis** On 15 occasions the urine was analyzed. Reaction was at all times acid. Specific gravity varied between 1.005 and 1.020. The sediment revealed rare hyaline casts during the first 10 days. During the last two weeks of life the sediment revealed many hyaline and a few granular casts. Red blood cells were rarely observed (4-6 H P F), whereas white blood cells varying from occasional to 15-100 were reported on all occasions. Sulfadiazine crystals were at no time seen.

TABLE I

| Blood   | R B C   | Hgb | W B C | Polys | Lymphs | Platelets |
|---------|---------|-----|-------|-------|--------|-----------|
| 7-13-43 |         | 63  | 3260  | 73    | 26     | 100,000   |
| 7-14-43 | 294     | 92  | 3950  |       |        |           |
| 7-15-43 |         |     | 4075  |       |        |           |
| 7-22-43 | 264     | 101 | 4200  |       |        |           |
| 7-23-43 | 27      | 101 | 1900  | 77    | 14     |           |
| 7-27-43 | 323     | 87  | 2150  | 66    | 32     |           |
| 7-29-43 | 222     | 86  | 2100  |       |        |           |
| 8-4-43  |         |     | 2800  | 67    | 31     |           |
| 8-5-43  |         |     | 3300  | 66    | 33     |           |
| 8-8-43  | 870,000 | 25  | 2070  |       |        |           |
| 8-12-43 |         | 52  | 1550  |       |        |           |
| 8-14-43 |         | 38  | 1000  | 1     | 99     |           |

TABLE II

| Blood   | BUN | Glucose | Total Protein | Blood Cultures                                 | Sedimentation Rate |       | Serology        |
|---------|-----|---------|---------------|--|--------------------|-------|-----------------|
|         |     |         |               |  | 1/2 hr             | 1 hr  |                 |
| 7-14-43 | 13  | 70      | 62<br>62      | Sterile  | 50 mm              | 55 mm | Hinton negative |
| 7-15-43 |     |         |               |  |                    |       |                 |
| 7-17-43 |     |         |               | Sterile  |                    |       |                 |
| 7-19-43 |     |         |               | Sterile  |                    |       |                 |
| 7-21-43 |     |         |               |  | 40 mm              | 58 mm |                 |
| 7-23-43 |     |         |               |  |                    |       |                 |
| 7-24-43 |     |         |               |  |                    |       |                 |
| 7-28-43 |     |         |               |  | 26 mm              | 35 mm |                 |
| 7-31-43 |     |         |               | Sterile  | 58 mm              | 63 mm |                 |
| 8-5-43  |     |         |               |  | 81 mm              | 85 mm |                 |
| 8-11-43 |     |         |               |  | 60 mm              | 78 mm |                 |
| 8-14-43 |     |         |               | Staph aureus<br>Very many colonies<br>Coag pos |                    |       |                 |

**Cultures** Nose and throat negative for hemolytic streptococcus (7-17-43) Feces negative for typhoid and dysentery group (7-20-43) Throat—*Streptococcus viridans* predominate (7-20-43) *Staphylococcus aureus* coagulase negative Smear from lesion in mouth (7-23-43) Few fusiform rods No spirillum seen

Other laboratory adjuncts Feces Guaiac negative (7-23-43) Old tuberculin test 1 10,000 negative on 7-27-43

**Röntgen-ray** (7-14-43) Examination of the chest showed slight accentuation of the structures in the region of the lung roots and accentuation of the markings particularly at the bases, but the lungs showed no active pathologic lesions There was no fluid in the pleural cavities The left cardiac contour was straighter than normal, and there was a slight bulge in the region of the left auricle which was consistent with rheumatic heart disease

**Electrocardiograms** (7-14-43) The tracing showed a rapid, regular action The P-R interval time was at the very upper limits of normal  $ST_1$ ,  $ST_2$  and  $ST_3$  showed slight elevation with upright T waves The record was somewhat abnormal and there were changes suggestive of an acute process Rate 110 (7-26-43) Since the tracing of 7-14-43 there had been some changes  $ST_1$  previously upright only slightly elevated now approached the base-line, and  $T_1$  previously upright was



inverted The second and third leads showed no significant changes, but in the fourth lead  $T_4$  previously upright was now inverted These changes were indicative of an acute process, and were not inconsistent with pericarditis Rate 104 (7-30-43) The action was rapid but regular Rate 117 There were two previous records, July 14 and 26 The changes were of minor significance The record still suggested a possible pericarditis

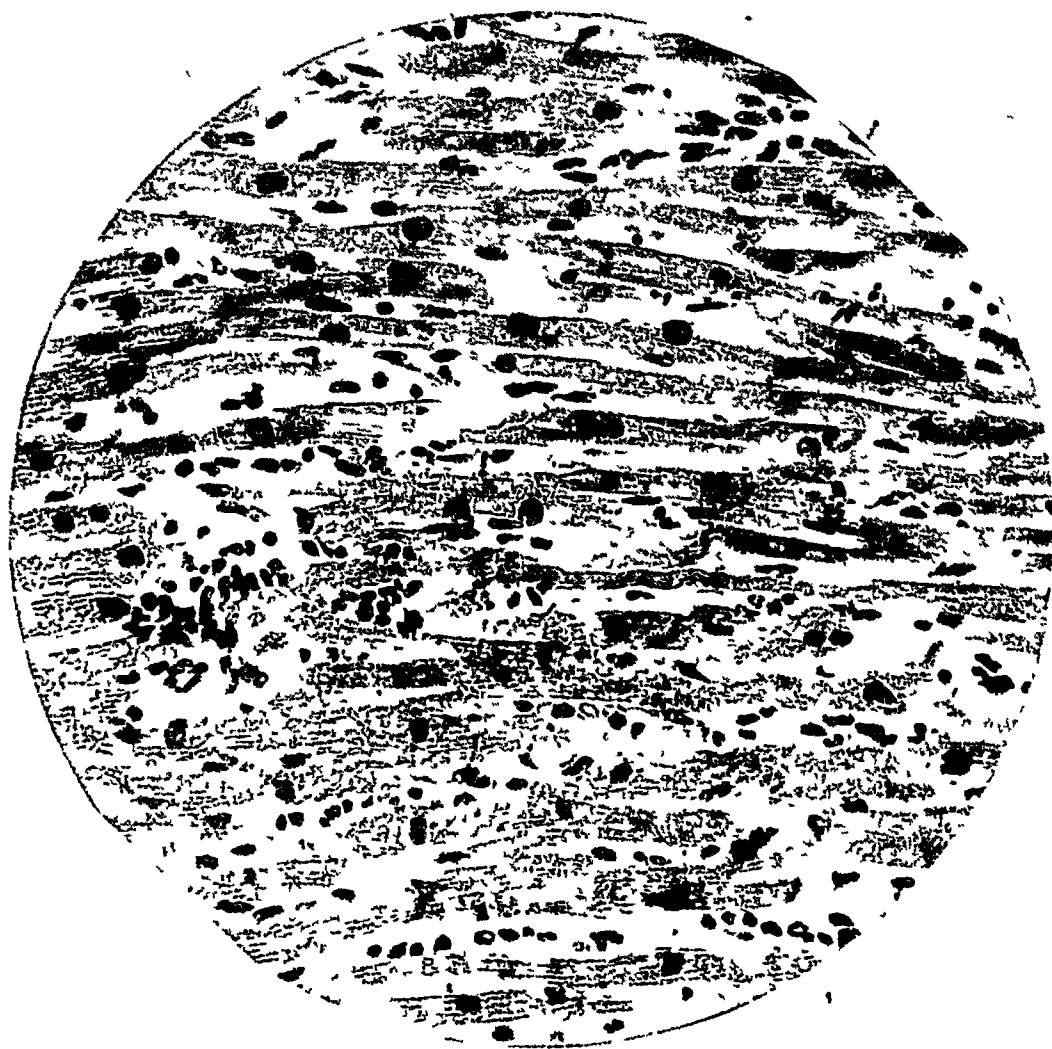


FIG 1 Heart Note the infiltration with lymphocytes containing pyknotic nuclei

*Autopsy Findings Gross Findings* The postmortem examination was performed two hours after death The body was that of a well developed, fairly well nourished white adolescent male measuring 175 cm in length The skin showed many fine transparent blebs over the body which measured up to 3 mm in greatest diameter There was an excoriated and crusted area at the base of the right nostril A decubitus ulcer, measuring 4 cm, was present on the right buttock

*Serous Cavities* The peritoneal cavity contained 200 cc of a light yellow fluid The peritoneum was thick white, and opaque The splenic flexure of the colon was adherent to the lateral wall Each pleural cavity contained 150 cc of a light yellow fluid The parietal pleura was thick, white, and opaque, and showed many petechial

hemorrhages throughout. The pericardial cavity contained 100 cc of a light yellow fluid. The pericardium, too, was thick, white, and opaque, and showed a few hemorrhagic areas measuring 3 mm in greatest diameter.

*Heart* The heart weighed 360 grams. The epicardium showed a number of petechial hemorrhages measuring up to 1 mm and two localized areas of thickened visceral pericardium measuring up to 2 cm. The endocardium of the auricles and left ventricle was generally thickened and opaque. The heart was entirely normal.

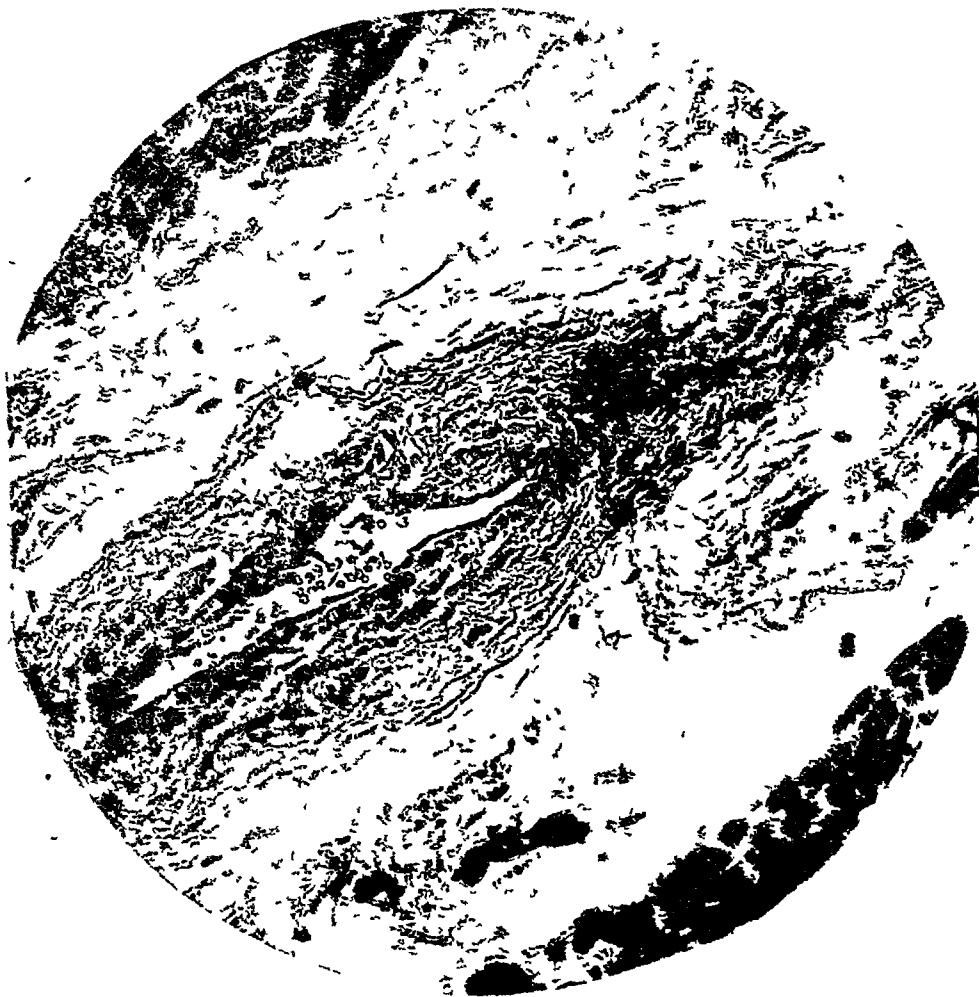


FIG 2 *Blood vessel in the myocardium.* The "fibrinoid degeneration" present in the adventitia of the vessel wall is especially prominent at the right of the lumen.

macroscopically except for the above findings and the mitral valve which, at its line of closure, showed two small, firm projections measuring 1 to 2 mm across. At the base of the mitral valve, just above its insertion, there were three similar larger areas measuring 3 mm across. The mitral valve generally was granular in appearance.

*Lungs* The lungs weighed 470 and 480 grams. On section, the parenchyma was a peculiar brownish color with numerous hemorrhagic areas measuring up to 1 cm in diameter.

*Spleen* The spleen weighed 360 grams. It was firm in consistency and its periphery showed irregular white, somewhat fibrous areas measuring up to 2 cm in diameter.

*Gastrointestinal Tract* The first part of the duodenum showed a number of hemorrhagic areas in the mucosa. The large intestine was filled with "tarry" fecal matter.

*Pancreas* The pancreas was firm in consistency and dark brown in color.



FIG 3 *Heart valve* Necrosis and hemorrhage may be seen in the subendothelial area. A thrombus is present which, at the left, is torn away.

*Liver* The liver weighed 1920 grams. The right border was mordinately pale and showed many small hemorrhages beneath its capsule measuring up to 1.5 cm. The lateral portion of the right lobe showed a typical "nutmeg" appearance.

*Kidneys* The right kidney weighed 270 grams, the left, 280 grams. The capsule was slightly adherent. The cortex was pale, measured up to 1 cm, and showed many small hemorrhagic areas.

*Bladder* The bladder was not remarkable.

*Aorta* The aorta was smooth and glistening and elastic.

*Brain* The brain weighed 1270 grams. Except for a small amount of sub-arachnoidal congestion, it was grossly not unusual. The pituitary was not remarkable.

*Bone Marrow* The bone marrow from the vertebrae was soft, almost liquid in consistency, and red in color. That from the upper one-third of the humerus was brown with some fat. The marrow from the ribs was red and scanty.

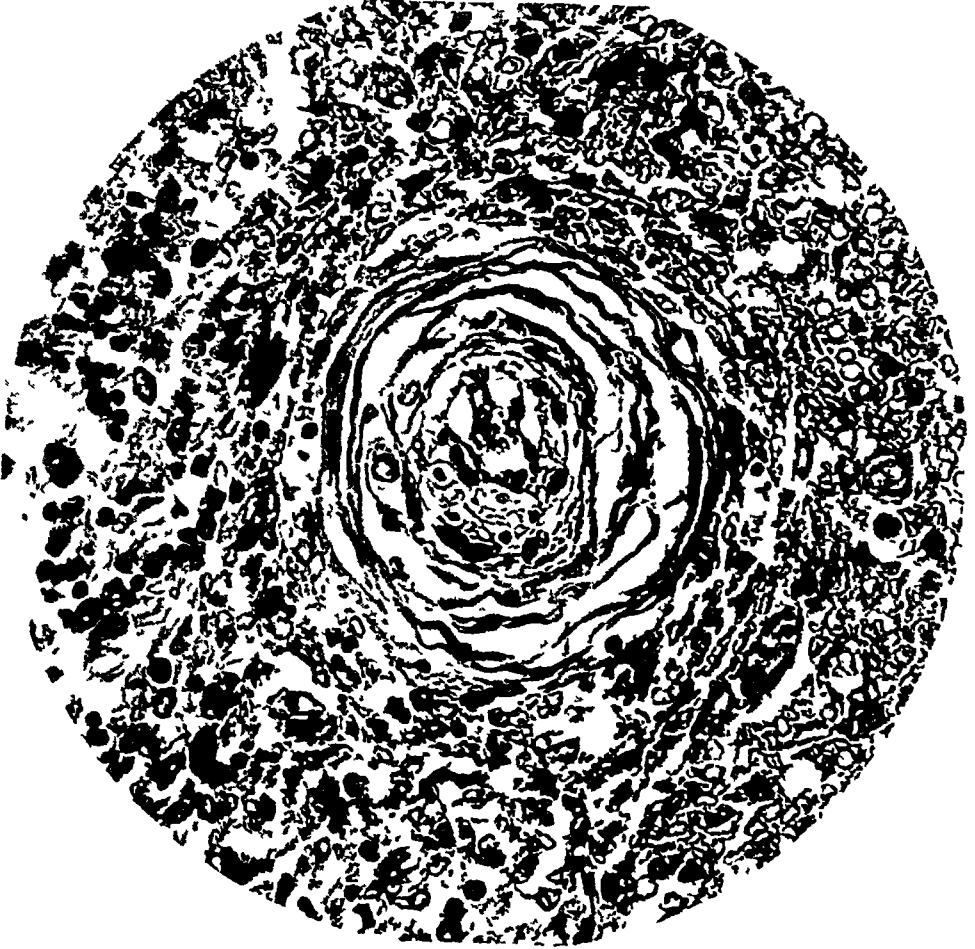


FIG 4 *Spleen* The periarterial fibrosis in "onion-skin" arrangement is especially prominent. Endothelial proliferation is present, almost completely occluding the lumen.

*Lymph Nodes* The mesenteric lymph nodes measured up to 1.5 cm and showed necrosis. A large group of nodes was present about the tail of the pancreas. These, too, showed necrosis.

*Thyroid* The thyroid gland was not unusual.

*Microscopic Findings Heart* The pericardium showed thickened collagenous material beneath its mesothelial surface. This showed granular, deeply eosinophilic masses of "fibrinoid degeneration" as described by Klemperer, Pollack, and Baehr.<sup>6</sup>

The epicardium showed "fibrinoid degeneration." In the myocardium was a sparse infiltration with lymphocytes and plasma cells with pyknotic nuclei (figure 1). The small and large vessels in the myocardium presented the appearance of 'fibrinoid degeneration' (figure 2). Sections of the lesions seen grossly in the mitral valve

showed the typical "fibrinoid degenerative" changes with one section revealing an organizing thrombotic process (figure 3) In one area was a slight amount of necrosis and hemorrhage beneath the endothelial surface There was no cellular reaction present No evidence of rheumatic fever was seen

*Lungs* In the blood vessels and peribronchiolar areas there was "fibrinoid degeneration" The alveolar walls were slightly thickened with an occasional leukocyte

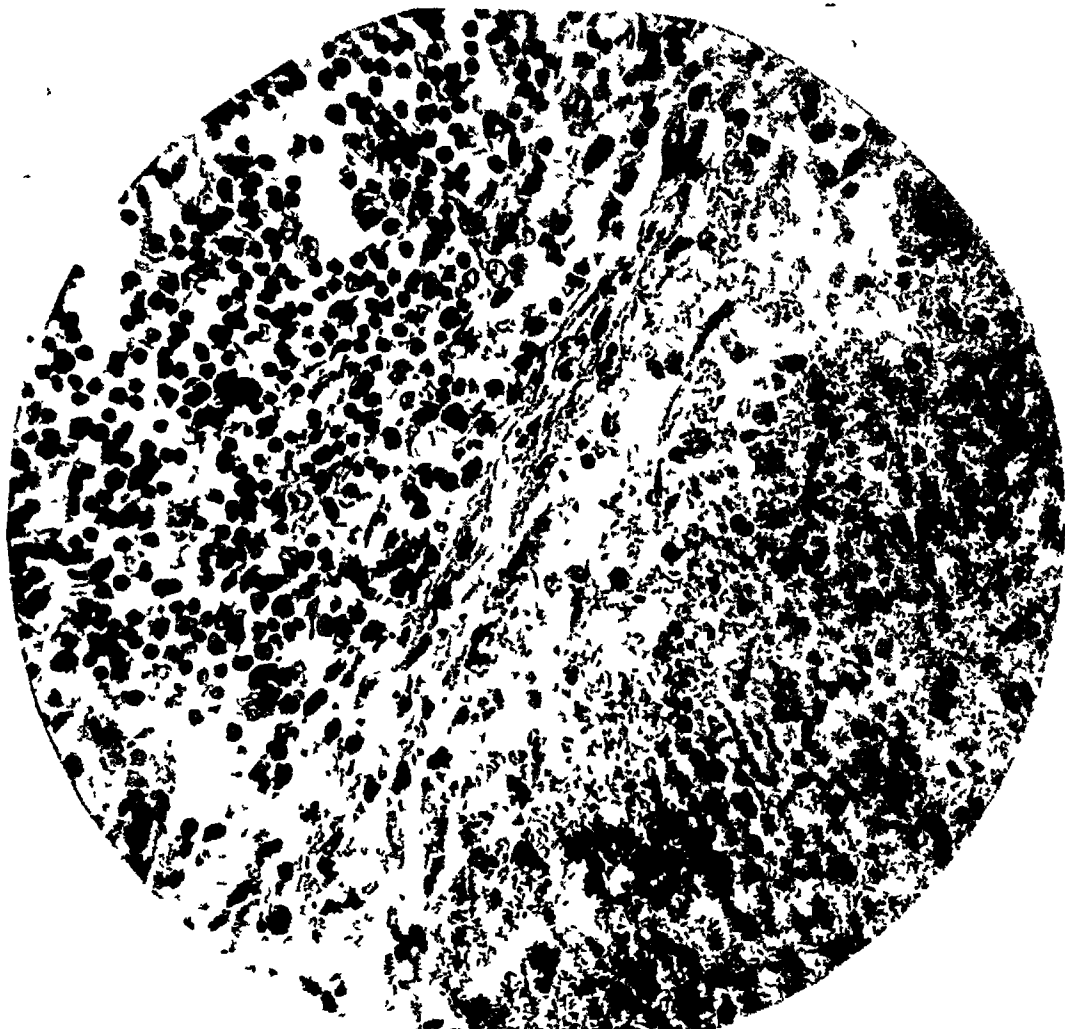


FIG. 5 *Lymph node* The necrosis is seen in the right-hand half of the photomicrograph

*Spleen.* The striking feature seen in the spleen was a peculiar periarterial fibrosis involving the central and penicilliary arteries This was arranged in concentric rings giving an onion-skin appearance (figure 4) A small amount of endothelial proliferation was seen in a number of the penicilliary arteries There was a generalized extravasation of red blood cells into the reticulum Large areas of necrosis were seen

*Gastrointestinal Tract* "Fibrinoid degeneration" was seen in the submucosa Some slight hemorrhage was present in the mucosa of the small intestine

*Pancreas* Some "fibrinoid" changes were seen in the perivascular areas and involving the trabeculae

*Liver* A marked amount of passive congestion destroyed the hepatic cells in the central area. Large masses of bacteria were present surrounded by necrosis but showing no leukocytic reaction. This peculiar finding may be explained by the bone marrow histology (see below). Again some slight "fibrinoid" changes were present in the portal areas.

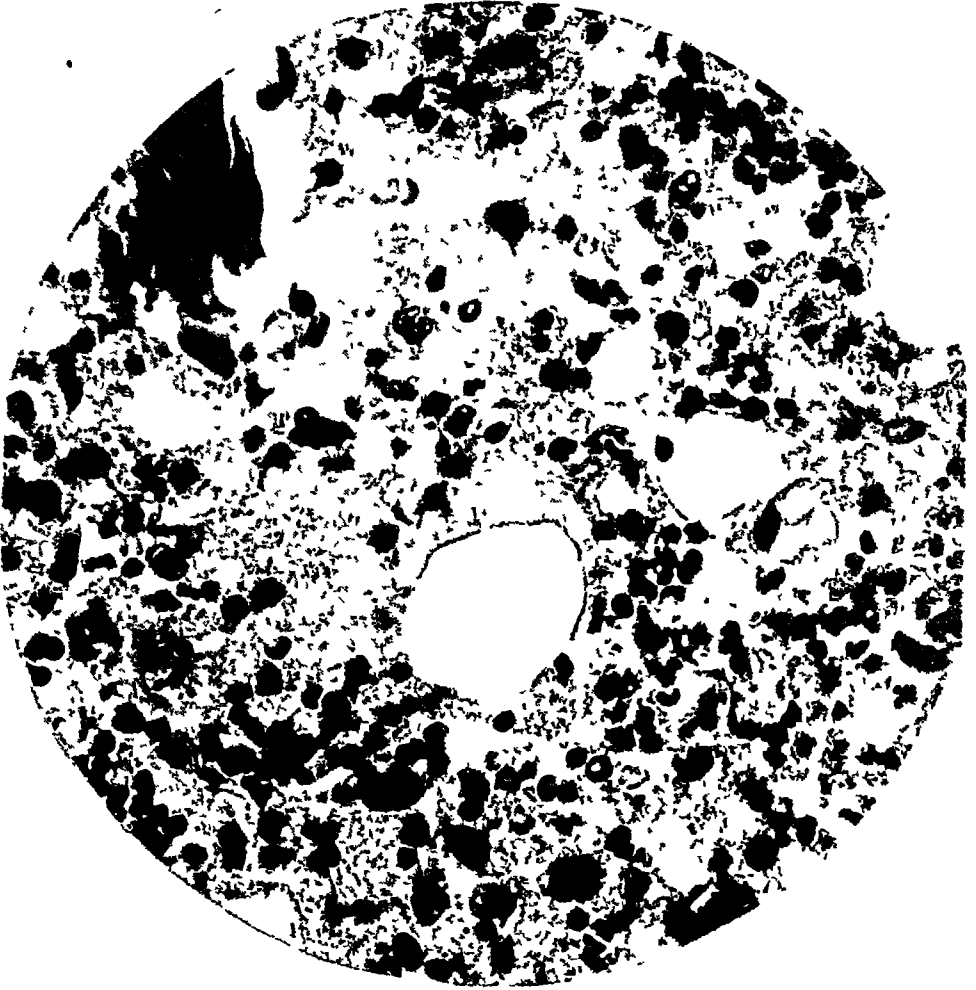


FIG 6 *Bone marrow* The cells are sparse with pyknotic nuclei and other degenerative changes. The granulopoietic series is almost entirely absent. The peculiar granular and gelatinous degeneration is present throughout the entire field.

*Kidneys* The glomeruli were cellular and avascular. Such capillaries as remained were congested. An occasional polymorphonuclear leukocyte was seen in the tuft. Some glomerular tufts showed a slightly thickened pericapillary connective tissue. These changes, we believe, are significant, even though they do not approach the "wire loop" appearance described by others. "Fibrinoid degenerative" changes were present around the vessels, but not as marked as in other organs. The acute glomerulitis was interpreted as being a part of the terminal staphylococcal septicemia.

*Adrenals* Some thickening of the capsule with "fibrinoid" changes was seen.

*Bladder* The "fibrinoid degeneration" seen elsewhere involved the bladder wall. This was especially marked in the submucosa and adventitial coats.

*Genitalia* The interstitial tissues of the testicle showed "fibrinoid" changes.

*Thyroid and Thymus* Both organs showed the changes in their connective tissues described in other organs.

*Bran* The meninges were thickened with "fibrinoid degenerative" alteration. The blood vessels had a marked eosinophilic staining reaction in their walls slightly resembling changes seen in periarteritis nodosa. No perivascular leukocytic reaction was present.

*Skin from Abdomen* "Fibrinoid" changes were again seen in the corium.

*Lymph Nodes* Necrosis was present in the majority of sections (figure 5). No evidence of tubercle formation was found.

*Bone Marrow* The predominant feature was a peculiar granular and gelatinous-like degeneration. A marked decrease in the granulopoietic series was seen and although small foci of erythropoietic tissue were present, the nuclei were pyknotic and showed karyorrhexis (figure 6).

*Diagnosis* Acute disseminated lupus erythematosus. Acute glomerulonephritis (early). Multiple petechial hemorrhages of the lungs. Interstitial bronchopneumonia. Necrosis of the spleen and lymph nodes. Interstitial non-suppurative myocarditis. Atypical verrucous endocarditis (Libman-Sacks). Focal necrosis of the liver. Chronic passive congestion of the liver. Hydroperitoneum, hydropericardium and hydrothorax (slight). Thickening of the pleura, pericardium and peritoneum. Multiple petechial hemorrhages of the pericardium, epicardium, pleura and liver.

*Comment on the Clinical and Pathological Aspect of the Case* Although the occurrence of this entity is unusual in a male subject, analysis of the clinical data and course would seem to justify the diagnosis of acute lupus erythematosus on a clinical basis alone.

Review reveals the following clinical aspects

- 1 Onset with polyarthralgia
- 2 Septic febrile course
- 3 Polyserositis
  - a Pleurisy
  - b Pericarditis
  - c Abdominal pain.
- 4 Gastrointestinal disturbance
  - a Anorexia
  - b Nausea
  - c Diarrhea
- 5 Bleeding tendency
  - a Oral and nasal bleeding
  - b Hemoptysis
  - c Rectal bleeding
- 6 Rapid, progressive course with fatal termination in an eight-week period

#### *Physical Findings*

- 1 Typical butterfly distribution of erythematous, scaly, atrophic lesion
- 2 Cardiac impairment

- a* Systolic murmur
- b* Gallop rhythm
- 3 General physical findings of a rapidly progressing, ravaging disease
- 4 Papilledema
- 5 Stomatitis and ulcerative pharyngitis
- 6 Lymphadenopathy

#### *Laboratory Findings*

- 1 Indicative of marked bone marrow depression
  - a* Severe anemia
  - b* Leukopenia
  - c* Thrombocytopenia
- 2 Renal damage (though not marked)
- 3 Persistently negative blood cultures until a terminal bacteremia
- 4 Electrocardiographic changes suggestive of pericarditis

The salient features in the gross pathological findings can be summarized in this manner

- 1 A generalized thickening of the serous membranes
- 2 Extravasation of fluid into the body cavities
- 3 Lymphadenopathy with necrosis
- 4 Non-bacterial verrucous endocarditis of the Libman-Sacks type

#### *The microscopic findings revealed*

- 1 A generalized involvement of collagen and ground substance in a change which Klemperer et al.<sup>8</sup> term "fibrinoid degeneration"
- 2 Confirmation of the gross findings of lymph node necrosis
- 3 Necrosis of the spleen
- 4 Periarterial fibrosis in the spleen
- 5 Changes in the glomerular tufts which might be termed minimal "wire looping"
- 6 A marked decrease in granulopoietic activity with a gelatinous-like degeneration in the bone marrow

The clinical and laboratory findings, the course of the disease, plus negative evidence as regards other entities, and finally confirmation by pathological examination would seem to warrant the diagnosis of acute disseminated lupus erythematosus

#### COMMENT

The definition "acute disseminated lupus erythematosus" would seem to us to be a most inaccurate and deceiving term. Most cases that are reported as acute lupus erythematosus disseminatus pursue a course varying from several weeks to several years with an approximate average duration of 18 months. The usual connotation of the word "acute" certainly, therefore, does not conform to the course of this disease.

The skin lesions are distinctly different in all respects from lupus vulgaris and, since a tuberculous etiology has been disproved to the satisfaction of most



students of the disease, it would seem that the term "lupus" has no place in the nomenclature

"Disseminated" is definitely in good usage and employed advisedly, however, it is used as descriptive of a term (erythema) that is a part of the clinical picture, but certainly an inconsequential part. The skin lesions do fall into that group of skin lesions classified as the erythemas

Many other terms have been suggested; however, none has been generally accepted as appropriate, which fact seems understandable when we take into account that we are attempting adequately to depict a disease of unknown etiology and characterized by such widespread and protean manifestations

The present terminology is of such long-standing usage, however, that further attempts to change nomenclature would only add to the confusion

The etiology of the disease continues to remain obscure and there is little to offer other than speculation and conjecture. The clinical features and course of clinical events vary greatly from case to case, however, in general the concept of a consistent clinical syndrome which permits diagnosis has been evolved

The subjective and objective clinical findings may be divided into two phases, one the result of a severe intoxication and the other phase reflected by signs and symptoms incriminating such various organs and systems as are in that particular case involved by the pathological process. The different symptoms and signs may and do vary greatly in their severity and one or more may be lacking in the case in question. This fact seems easily understandable when one reflects that the pathological process may involve any organ or system of the body to a varying extent. Thus, it would seem feasible that the symptoms vary as do the site and extent of the pathologic lesions. Certain organs do appear to be sites of predilection and, in general, whatever the symptoms of the individual case, they seem to be grafted on a background of a severe toxic state

The present case being reported as one of acute lupus erythematosus disseminatus with associated atypical verrucous endocarditis or Libman-Sacks syndrome brings forth an interesting point of discussion concerning the latter. This condition was first recognized and commented upon by Libman<sup>9</sup>. He observed what he termed an atypical verrucous endocarditis while in the course of his study of endocarditis, as early as 1911. This condition, although pathologically showing resemblance to the endocarditis of both rheumatic fever and subacute bacterial endocarditis, nevertheless differs in certain fundamental features. Libman-Sacks<sup>7</sup> in 1924 described in detail four cases of this condition which they considered as a distinct clinical entity

Belote and Ratner<sup>10</sup> have recently questioned its existence as a nosologic entity. That this condition differs from the endocarditis of rheumatic fever and subacute bacterial endocarditis is doubtless universally recognized and such recognition is based on sound clinical and pathological evidence. However, its status as a distinct entity unto itself, which is likewise generally recognized, would seem to us to be open to doubt, or at least grave suspicion. When the clinical and pathological details noted in a case of acute lupus erythematosus disseminatus are compared with similar details from cases of atypical verrucous endocarditis, it is observed that they are fundamentally the same. The only constant difference is the occurrence of the endocarditis and at times the associated embolic phenomenon found in the Libman-Sacks syndrome

Gross<sup>11</sup> compared the pathological changes in the hearts of 23 cases of acute lupus erythematosus disseminatus with those found in four cases of so-called Libman-Sacks disease with lupus erythematosus. Macroscopic changes were present in nine of the former group and microscopic changes in almost all of the cases. His conclusion was that the changes were characteristic of those found in the Libman-Sacks group, that in some instances they were identical, and that the two diseases were essentially the same and should be, therefore, under the one heading—namely, Libman-Sacks disease.

The skin lesions of the two conditions have been declared histologically alike by several competent observers. O'Leary,<sup>12</sup> in the discussion of Belote and Ratner's paper, states this fact. Likewise, it has been found in general that the pathology of these two conditions is fundamentally similar if not identical.

Gross<sup>11</sup> concluded the two conditions to be essentially the same but advocated that the condition of acute lupus erythematosus be considered under the single heading of Libman-Sacks disease. Ginzler and Fox<sup>13</sup> commented on the similarity between the two conditions as regards the clinical features. Rose and Pillsbury<sup>14</sup> state "It seems beyond doubt that those cases described by Libman and Sacks with erythematous facial lesions were examples of acute lupus erythematosus disseminatus with visceral involvement." Belote and Ratner<sup>10</sup> report a case considered as an example of the Libman-Sacks syndrome and after careful study believe this entity should be classified as a sub-variety of the cases presented by Osler. We believe that the condition of acute lupus erythematosus disseminatus, Libman-Sacks disease, and at least some of the cases reported by Osler are all examples of the entity first appreciated by Kaposi and termed by him "lupus erythematosus discretus and aggregatus."

Certainly it would seem more plausible to consider that there have been cases of the so-called Libman-Sacks syndrome that prior to 1911 were overlooked because the case in question did not feature the endocardial changes or that, if present, they were missed because of lack of autopsy material or detailed microscopic study, than to believe that there is a newly discovered disease that is generally conceded to be fundamentally similar in all respects to an entity previously described by several competent workers.

#### DISCUSSION OF THE PATHOLOGY

Klemperer, Pollack, and Baehr,<sup>8</sup> in 1941, discussed thoroughly and adequately the pathological findings in diffuse lupus erythematosus. Through their efforts, the pathologic criteria have been simplified and coordinated. Certain conspicuous changes have been described in the heart, spleen, blood vessels, serous membranes, and kidneys. These changes appear to show a common morbid process—an alteration affecting the connective tissue throughout the body, the so-called "fibrinoid degeneration." This change can affect any organ in varying degrees, accounting for the protean manifestations of the disease's clinical course and the absence of typical findings in some organs at postmortem examination. The serous membranes are usually thickened. There is often a pleuritis, pericarditis, and peritonitis of a fibrinous or fibrous type. Frequently effusions are present.

The heart is usually enlarged. The valves not infrequently present the picture of a Libman-Sacks endocarditis with the histopathological picture varying from a simple sub-endothelial "fibrinoid degeneration" to hemorrhage,

necrosis, and thrombus formation. We feel that the Libman-Sacks atypical verrucous endocarditis is not a disease entity within itself, but rather a localized manifestation in the endocardium of the generalized alteration in the ground substance. Two possible mechanisms of pathogenesis present themselves: (1) The "fibrinoid degeneration" involving the capillaries supplying the valves causes an endarteritis with hemorrhage and necrosis and subsequent thrombus formation, (2) the "fibrinoid degeneration" and endothelial proliferation of the endocardium itself allow platelet deposition upon the surface with later organization and thrombus formation. The lesions in the case presented were of the "pyramidal-ridge" type<sup>15</sup>. Microscopically they showed an advanced type of lesion with necrosis, hemorrhage, and thrombus formation (figure 3). The blood vessels in the myocardium, as elsewhere, often show "fibrinoid degeneration" in their adventitial coats (figure 2).

"Periarterial fibrosis" is seen almost constantly in the spleen. Klemperer et al.<sup>8</sup> state, "periarterial sclerosis found in nearly every case is so arresting that it must be considered specific." Kaiser,<sup>16</sup> however, recently describes these lesions in thrombocytopenia and other widely dissociated diseases as well as in disseminated lupus erythematosus. His conclusions, while against the specificity of this lesion, do not militate against its use as a positive diagnostic finding when used in conjunction with the clinical history and other pathological findings. Hemosiderosis, hyperplasia, and congestion are not unusual in the spleen. Our case showed marked and typical periarterial fibrosis (figure 4).

Enlargement and necrosis of the lymph nodes is generally described as a fairly consistent finding. Fox and Rosahn<sup>17</sup> found in their series of 280 cases that lymphadenopathy was present in 66.7 per cent. The histopathological picture was one of edema with engorgement and, not infrequently, necrosis. They felt that these lesions were "suggestive of, but not specific for, the disease." Necrosis of the lymph nodes was a prominent feature in our case (figure 5).

The finding of "wire-loops" in the kidney has been described as being diagnostic of disseminated lupus erythematosus. This is considered to be fibrinoid degenerative changes in the glomerular arteriolar wall. Some cases show none of this distinctive change and we must consider that the kidney was spared the onslaught of the morbid process. Necrosis of the glomerular loops is also described. Glomerulonephritis has been reported in a number of cases and was present in our case, probably as a result of the terminal staphylococcal bacteremia. We found no evidence of fully developed "wire-loops" in our case, but felt that the changes present might be minimal changes. The liver has been reported as showing the picture of focal necrosis. No explanation has been advanced beyond a possible terminal bacteremia. Our case showed just such changes.

The brain often shows edema and a degenerative process. In our case there was an involvement of the blood vessel wall which resembles changes seen in periarteritis nodosa.

The bone marrow is usually described as normal or hyperplastic, even in those cases in which a leukopenia is seen clinically. The case presented showed a picture of marked granulopoietic depression with a peculiar gelatinous-like degeneration (figure 6). We feel that this is the reason for the lack of a leukocytic response to the bacteria and necrosis in the liver. Although tuberculosis as an etiological agent has been disproved,<sup>9</sup> it is occasionally seen at necropsy.

It is possible that in the past the necrosis which is often widespread in the lymph nodes has been mistaken for the caseous process of tuberculosis. There was no evidence of tuberculosis in our case.

### SUMMARY

We have reported a case in a male which from its clinical signs and symptoms, course, and pathological findings, and lack of any other tenable diagnosis warrants the diagnosis of acute disseminated lupus erythematosus with atypical verrucous endocarditis (Libman-Sacks).

The findings as recorded and a review of the literature lead us to question the existence of a separate clinical entity termed the "Libman-Sacks syndrome" and to suggest that it is a local manifestation of an extensive and widespread pathologic process described previously as acute disseminated lupus erythematosus.

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### BIBLIOGRAPHY

- 1 HEBRA, F. *Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien*, 1845, 1, 40. Cited by KLEMPERER ET AL.<sup>8</sup>
- 2 CAZENAVE, A. *Ann. d. mal. de la peau*, 1851, III, 297. Cited by KLEMPERER ET AL.<sup>8</sup>
- 3 KAPOSI, M. *Arch. f. Dermat. u. Syph.*, 1872, IV, 36. Cited by KLEMPERER ET AL.<sup>8</sup>
- 4 OSLER, W. On the visceral manifestations of erythema exudativum multiforme, *Am. Jr. Med. Sci.*, 1895, CX, 629.
- 5 OSLER, W. The visceral lesions of the erythema group (2nd series of cases), *Brit. Jr. Dermat.*, 1900, XII, 227.
- 6 OSLER, W. On the visceral manifestations of the erythema group of skin diseases, *Am. Jr. Med. Sci.*, 1904, CXXVII, 1.
- 7 LIBMAN, E., and SACKS, B. A hitherto undescribed form of valvular and mural endocarditis, *Arch. Int. Med.*, 1924, XXXIII, 701.
- 8 KLEMPERER, P., POLLACK, A. D., and BAEHR, G. Pathology of disseminated lupus erythematosus, *Arch. Path.*, 1941, XXXII, 569.
- 9 LIBMAN, E. Some general considerations concerning affections of the heart valves, *Med. Clin. N. Am.*, 1917, 1, 573.
- 10 BELOTE, G., and RATNER, H. S. The so-called Libman-Sacks syndrome. Its relation to dermatology, *Arch. Dermat. and Syph.*, 1936, XXXIII, 642.
- 11 GROSS, L. Unpublished data, cited by FRIEDBURG, C., GROSS, L., and WALLACH, K. Nonbacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions, *Arch. Int. Med.*, 1936, LXVI, 662.
- 12 O'LEARY, discussion of paper by BELOTE and RATNER.<sup>11</sup>
- 13 GINZLER, A. M., and FOX, T. T. Disseminated lupus erythematosus—a cutaneous manifestation of a systemic disease (Libman-Sacks), *Arch. Int. Med.*, 1940, LXX, 26.
- 14 ROSE, E., and PILLSBURY, D. M. Acute disseminated lupus erythematosus—a systemic disease, *Ann. Int. Med.*, 1939, XII, 951.
- 15 GROSS, L. The cardiac lesions in Libman-Sacks disease with consideration of its relationship to acute diffuse lupus erythematosus, *Am. Jr. Path.*, 1940, XLVI, 375.
- 16 KAISER, I. The specificity of periaarterial fibrosis of the spleen in disseminated lupus erythematosus, *Bull. Johns Hopkins Hosp.*, 1942, LXXI, 31.
- 17 FOX, R., and ROSAHN, P. D. The lymph node in disseminated lupus erythematosus, *Am. Jr. Path.*, 1943, XLIX, 73.

## COMPARATIVE ELECTROCARDIOGRAPHIC CHANGES IN ANGINA PECTORIS AND CORONARY THROMBOSIS IN THE SAME PATIENT; REPORT OF A CASE \*

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THE literature records a relatively small number of cases of fleeting electrocardiographic changes in the course of an attack of spontaneous cardiac pain<sup>1, 2, 3, 5, 6, 7, 8</sup> Observations have been made to correlate these changes with those occurring following a coronary occlusion, both experimentally<sup>4</sup> and clinically<sup>9</sup> An unusual opportunity presented itself to make observations relative to this matter in a patient with coronary artery disease, who while giving an account of the character of his recurrent attacks of precordial pain, developed the symptoms he was trying to describe Four hours later he developed a more severe and persistent attack of pain which proved to be coronary thrombosis Electrocardiograms were obtained during the fleeting attack of pain, two minutes after it had subsided, and at various intervals during and subsequent to the attack of coronary thrombosis Such a sequence of events in one and the same patient recorded electrocardiographically is not a common experience The record of this case is the subject of this report

### CASE REPORT

A 57 year old white male related that he had first experienced precordial pain on effort five years ago These spells of pain recurred for several months, but since then he had been symptom free On the morning in question he noted a recurrence of precordial pain on effort which lasted several minutes, and disappeared abruptly While describing the attack he was suddenly seized with pain over his precordium Advantage was taken of this opportunity to record an electrocardiogram while the pain persisted Only three leads could be taken before the pain disappeared (figure A) S-T segment depression is noted in all three leads About two minutes after he was relieved of his distress the three standard leads and an apex lead were repeated (figure B) All S-T segments have returned to the isoelectric line and a normal tracing is evident

Examination of the patient at this time revealed no abnormal findings His color was good The pulse was of good quality Regular rhythm was present, there were no murmurs, and the blood pressure was 140 mm Hg systolic and 90 mm diastolic Fluoroscopy revealed no abnormalities in the size and shape of the heart and aorta

Four hours later, during the night, the patient was awakened from his sleep with severe precordial pain This was more severe than the previous attacks, and more persistent The heart sounds were poor, rhythm was regular, pulse was 88 per minute By morning his pain had abated somewhat An electrocardiogram taken at this time (figure C) shows depression of the S-T segment in Leads II and III The ensuing course followed the pattern of an acute myocardial infarct The temperature reached the high level of 102° F within the next several days and returned to normal on the eighth day The blood pressure fell to 108 mm Hg systolic and 80 mm diastolic, and returned to 130 mm systolic and 90 mm diastolic at the end of the fourth week He exhibited an increased sedimentation rate until after the fifth week Serial electrocardiograms are presented to illustrate the changing pattern (figures D, E)

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From the Cardiac Service of Dr Harry Gold, The Hospital for Joint Diseases

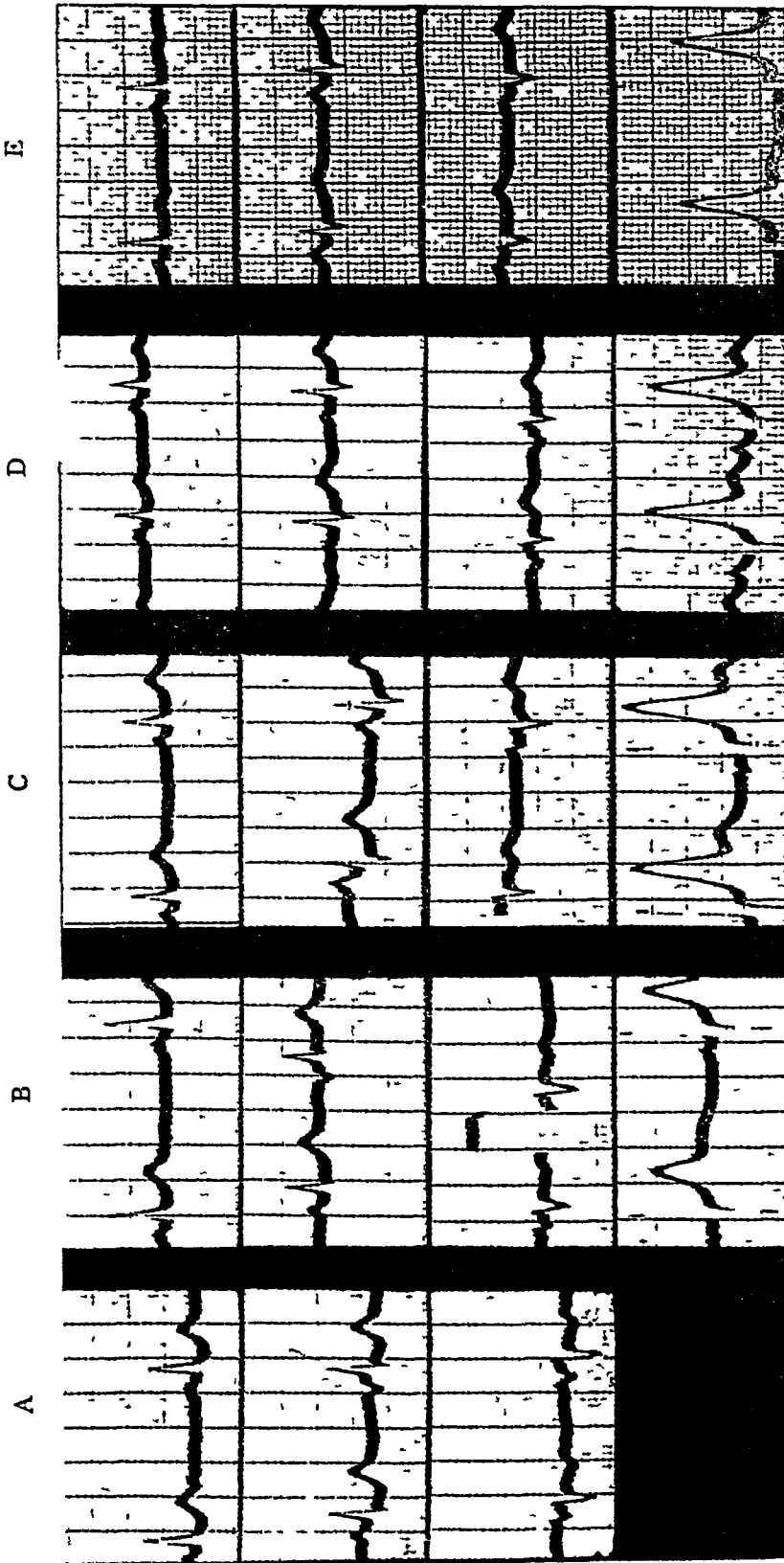


FIG 1 *A* Three standard leads taken during a spontaneous attack of angina pectoris. Shows depression of the S-T segments in all leads. *B* Three standard leads and an apex lead taken after relief from the anginal attack. Shows return of the S-T segments to the isoelectric line. *C* Electrocardiogram taken eight hours after an attack of coronary thrombosis, approximately 12 hours after figure *B*. Shows S-T segments in Leads II and III depressed below the isoelectric line. *D* and *E* Serial electrocardiograms taken the following day and 13 days later respectively. This illustrates the changing pattern as seen in coronary occlusion, rather than the return to normal as seen in figure *B* following the recovery from the anginal attack.

## COMMENT

The electrocardiographic changes occurring during the course of functional cardiac pain showed the same pattern as those in the early phases of coronary thrombosis, which occurred four hours later. It is noteworthy to point out, however, that the changes were more extensive during the pain of the functional episode than during the terminal phase of the pain due to the organic episode, since S-T segment changes occurred in all three standard leads during the former, and only in Leads II and III during the latter. One can only speculate concerning the significance of these differences. The initial electrocardiogram was taken during the severe pain of the anginal attack and may, therefore, be indicative of the generalized reflex myocardial ischemia which takes place, although it is fleeting. On the other hand, the electrocardiogram taken following the coronary thrombosis was taken after the severe pain had subsided, which may in turn indicate a lesser degree of reflex spasm, and, therefore, a lesser degree of generalized myocardial ischemia.

One may also emphasize the fact, to which attention has been called repeatedly in the literature, and as clearly demonstrated in this case, that a normal electrocardiogram does not preclude advanced coronary artery disease. This patient showed a normal electrocardiogram two minutes after one demonstrating severe myocardial ischemia, and four hours before a coronary thrombosis.

## BIBLIOGRAPHY

- 1 BOUSFIELD, G. Angina pectoris, changes in electrocardiogram during a paroxysm, *Lancet*, 1918, ii, 457-458.
- 2 FEIL, H, and SIEGEL, M. L. Electrocardiographic changes during attacks of angina pectoris, *Am Jr Med Sci*, 1928, clxxv, 255-260.
- 3 PARKINSON, J, and BEDFORD, E. D. Electrocardiographic changes during brief attacks of angina pectoris, *Lancet*, 1931, i, 15-19.
- 4 WOOD, F. C, and WOLFERTH, C. C. Angina pectoris. The clinical and electrocardiographic phenomena of the attack and their comparison with effects of experimental coronary occlusion, *Arch Int Med*, 1931, xlvii, 339-365.
- 5 HALL, D. Electrocardiograms of two patients during attacks of angina pectoris, *Lancet*, 1932, i, 1254-1255.
- 6 TURNER, H. B. Transient alterations in the electrocardiogram during an attack of angina pectoris terminated by the inhalation of amyl nitrite, *Jr Am Med Assoc*, 1933, c, 38-39.
- 7 SHAPIRO, H. H, and SMYTH, L. A. Transient electrocardiographic changes noted during an attack of angina pectoris with report of a case, *Jr Lab and Clin Med*, 1938, xxiii, 819-822.
- 8 BROW, G. R, and HOLMAN, D. V. Electrocardiographic study during a paroxysm of angina pectoris, *Am Heart Jr*, 1933, ix, 259-269.
- 9 WILSON, F. N, and JOHNSTON, F. D. The occurrence in angina pectoris of electrocardiographic changes, *Am Heart Jr*, 1941, xxii, 64-74.

**EQUINE INFECTIOUS ANEMIA TRANSMITTED TO MAN \***

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IN his recent book, titled "Diseases Transmitted from Animals to Man" (1941), Thomas Hull<sup>1</sup> writes "equine infectious anemia has never been known to infect man" The purpose of this report is to demonstrate that this statement is no longer valid It is not difficult to recognize this virus disease if the possibility of its occurrence be remembered It may be expected that other cases will soon be discovered among patients with aplastic anemia of unknown origin if the method of examination described in this article be applied This expectation is based on the following facts *a* There is a large number of infected horses and mules in the United States and elsewhere The disease in horses tends to occur in certain large areas In the United States, according to Hagan<sup>2</sup> (1943) many horses in the northern and western states and many mules in the Mississippi Delta region die from this disease *b* Insects, which are well-known "blood-suckers" in man, are at the same time transmitters of equine infectious anemia *c* Some forms of aplastic anemia of unknown origin are strikingly similar to the anemia which was observed in the case described below

**CASE REPORT**

The patient, who was a professor of pathology and hematology at a School of Veterinary Medicine, had himself made the diagnosis of infectious anemia He was convinced that physicians knew much less about the disease than he did Therefore he had refused all aid and examinations by physicians However, the author succeeded in persuading him that a comparison of his symptoms and signs with those associated with certain anemias, described in man, might add significantly to our knowledge of these diseases The patient consented to be examined, but under these circumstances the author could not perform certain examinations (e.g., bone marrow studies) which the patient considered to be unnecessary

The patient, a man 45 years of age, was a veterinarian who often came in contact with horses suffering from equine infectious anemia The patient was never sick before this, and his family history was irrelevant His chief complaint was weakness The present illness began two years previously when a skin eruption which the patient called a "herpetiform exanthema" appeared in the umbilical region It soon disappeared At that time diarrhea alternating with constipation occurred A few weeks after the onset of the disease a slight edema appeared, extending over the whole body but most evident in the eyelids There was no albuminuria Between the attacks there were short intervals when the patient felt well However, constant weakness and pallor of the skin developed Severe headaches were frequent and were localized usually in the occipital region Now and then fever occurred, but was never of a high grade After a few months the intervals of relative well-being returned and were longer than before, but the recurring attacks were just as severe

*Laboratory findings* The urine revealed no pathological findings The blood was examined on numerous occasions by the patient himself Hemoglobin was approximately 30 volumes per cent (Sahli), that is about 4.3 gm per cent The num-

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ber of red cells per cu mm was about two millions. The mean corpuscular hemoglobin was 23 and the color index 0.8. Normoblasts and megaloblasts were never found. Poikilocytosis and anisocytosis were always present. The number of leukocytes varied from 1800 to 2600 per cu mm. The differential count revealed no abnormalities except a relative lymphocytosis. The number of the platelets was within normal limits, but many were so-called "giant platelets." This is perhaps of diagnostic importance. The patient had an intestinal hemorrhage during only one of the exacerbations. Between the attacks no hemorrhage occurred. The following negative findings may be mentioned. The lungs and heart showed no abnormal findings, except anemic systolic murmurs over all the ostia. The blood pressure was always within normal limits. The liver and spleen were not enlarged. Jaundice was absent and there was no increased loss of urobilin and urobilinogen. There were no aphthae on the tongue. There was no tenderness on pressure over the sternum or other bones.

*Physical examination* This revealed no data of importance which have not been mentioned. In order not to present a confused picture, it seemed better to mention in this article only the symptoms and laboratory findings observed during the peak of the disease because only these enable the examiner to make the right diagnosis.

From the onset of the symptoms—as mentioned above—the patient had made the diagnosis of equine infectious anemia in himself because his symptoms were similar to those observed in infected horses. He was convinced that he had to die from this disease which he called by the older name "pernicious anemia." He saw this outcome in the majority of the infected horses. The proof that his diagnosis was correct was demonstrated by the following test which is used regularly in horses. The patient injected 1 c.c. of his blood intravenously into a young strong horse. The animal died from equine infectious anemia. This crucial test was repeated with the same result in two other young healthy horses. He carried out these tests with filtered and unfiltered blood with identical results. This excluded other diseases not caused by a virus. For nearly two years the poor condition of the patient remained unchanged. At the beginning of the third year, during which the author examined the patient, an amelioration of the disease appeared. The first sign was that the intervals between the attacks became longer. Of great importance was the fact that a horse, injected with the patient's blood, remained healthy. This was repeated in other horses with the same result. The reason this repetition was necessary is the existence of "healthy" equine carriers which will be discussed later.

However, in spite of the fact that his blood was negative, his prognosis remained unfavorable because he knew cases in horses which were apparently healthy and whose blood remained negative during long periods, yet after 10 years or more new attacks developed in one of which the animal died.

From the blood picture, described above, it is obvious that the patient had an aplastic type of anemia which involved the myeloid and erythrogenic tissues but not the platelets. Such forms of anemia are known to occur in man. In the hematologic literature this form of anemia in man is described under the heading "Atypical Forms of Aplastic Anemia." One of these forms was called by Downey<sup>3</sup> in 1938 "Aplastic Anemia without Thrombocytopenia." Giant platelets are found in human blood in chronic infections. They may become so large that they are confused with flagellates. This happened to the author as he saw these platelets for the first time. This possibility should be remembered in future cases. There is certainly sufficient reason to carry out an inoculation of a horse with the blood of a patient who is suffering from "aplastic anemia without thrombocytopenia" with giant platelets. If it is negative a second horse should be inoculated for reasons given below. However, even if thrombocytopenia

is present with or without giant platelets, one should carry out this test because in horses there are variations which may occur also in man. In the chronic form of aplastic anemia in man hemorrhage is rare, in sharp contrast with the well-known occurrence of hemorrhage in the acute form. This is in accordance with this patient's symptoms.

Since this virus infection has to be added to the "human diseases" it is of importance to know what has already been discovered concerning this disease and also to know the gaps in our knowledge which still have to be filled in. For this purpose the author used Hagan's *Infectious Diseases of Domestic Animals - Runnells' Animal Pathology*,<sup>6</sup> and an article of C. Stein et al.<sup>7</sup>

In 1904 the French investigators Carré and Vallée discovered that the etiologic agent of this disease was a filtrable virus. They showed that filtrates, passed through Berkefeld filters, could infect other horses. The virus was found in blood, urine and feces. Its length is between 18 and 50 millimicra. It is very resistant to disinfectants, freezing, and desiccation, and is little affected by age. Dried blood retains virulence for several months, if protected from sunlight. Of great importance for the possibility of an infection in man is the fact that the disease is spread principally through the agency of insects. The chief offenders are the blood-sucking common stable fly, *Stomoxys calcitrans* and the mosquito *Anopheles maculipennis*. It is probable that the *Anopheles quadrimaculatus*, the malaria-transmitter in the United States, also transmits infectious anemia. This is all the more probable since this infection can be transmitted mechanically by the bite. Scott showed that infection in horses could be produced by a single prick with a hypodermic needle which was contaminated by pricking an infected horse. There is some evidence that horses can also be infected by feeding from the same floor or from common containers. However, the principal transmitters are insects. There are no reports of successful cultivation of the virus in artificial media. Therefore, the only way to detect the many apparently healthy virus-carriers among horses is to inoculate their blood into other horses. However, the fallacy in this experiment is that the selected animal may already be a carrier and, therefore, may not react. For this reason, if the first test is negative, it is necessary to inoculate a second horse in order to make the chance of error smaller. The discovery of a suitable artificial culture medium would be of priceless value, not only for the diagnosis in horses, but also for the routine examination of blood in human aplastic anemia. Here lies an open field for a bacteriologist.

If an inoculated test-horse is susceptible, it presents fever usually within 15 to 30 days. The most constant findings are a rapid decrease in hemoglobin and red cells, an increase in the sedimentation rate and in the plasma globulins. The blood changes are more or less variable, as already mentioned.

It can be expected that after this war, there will be a further spread of the disease in horses. After every war this phenomenon has occurred. Horses are assembled, during wars, from many areas. The return of horses to civilian life is likely to set up new foci.

In horses there is an acute, subacute and chronic form of infectious anemia. In the acute form death may occur within a few days. The subacute form may lead to death within three months. Both forms may go into the chronic form which is often interrupted by acute exacerbations, during any of which death may occur. The blood usually remains infectious, but may become temporarily

free from the virus. Some investigators believe that recovery in horses never occurs, but this conception is incorrect according to others. How treacherous this disease is, at least in horses, is shown by the history of a horse described by Schalk and Roderick.<sup>5</sup> This horse was used as a test-animal. It had several acute attacks during the first three years, but then lived apparently in good health for 14 years. Every year the blood was inoculated into another horse. All of these inoculated horses, except one, developed the disease. Then suddenly the horse died in an acute attack.

The results of inoculations of rabbits and birds have been unreliable, because these animals often seem to be immune. Means of immunization have not yet been developed, in spite of many attempts. The problem of therapy is unsolved.

### SUMMARY AND CONCLUSIONS

1 Equine infectious anemia can be transmitted to man.

2 The blood of patients with the so-called idiopathic aplastic anemia should be inoculated in horses in order to diagnose this disease in man. This test should not be considered too expensive because it is probably harmless for the animal if the patient does not have infectious anemia, and it is of great diagnostic importance if the horse develops the disease. It can easily be done in the larger veterinary institutions because in such places this inoculation is a routine test for the diagnosis of the disease in horses. (The author has received a letter from the Veterinary Institution in Washington, D. C., stating that blood from a suspected case would there be injected into a healthy horse.)

3 The probability that cases will soon be detected in man is emphasized, especially if adequate culture media for the virus are found. This opinion is supported by three facts: (a) The large number of infected horses and mules; (b) The insects which transmit the disease among horses are the same which are known to bite man. Merely contact of the sting contaminated with infected blood is sufficient for the transmission of the disease; (c) A description of the anemia which the patient had can be found in all textbooks of medicine under the heading "Idiopathic Aplastic Anemia" which is not a rare disease. At the present time the only reliable method of making the diagnosis of this disease is the inoculation of horses with blood of the patient.

### BIBLIOGRAPHY

- 1 HULL, THOMAS G. Diseases transmitted from animals to man, 2d ed, 1941, Thomas.
- 2 HAGAN, W. A. Infectious diseases of domestic animals with special reference to etiology, diagnosis and biologic therapy, 1943, Comstock.
- 3 DOWNEY, H. Handbook of hematology, 1938, Hoeber, vol. 3, p. 2171.
- 4 VAILLE and CARRE. Sur la nature infectieuse de l'anémie du cheval, *Compt. rend. Acad. d. sci.*, 1904, *CXXXIX*, 331-333.
- 5 SCHALK, A. F., and RODRICK, L. M. The history of swamp fever virus carrier, *South Dakota Agric. Exper. Station Bull.* 168, Agric. College North Dakota, 1923.
- 6 RUNNELS, R. A. Animal pathology, 2d ed 1941, Iowa State College Press.
7. STEIN, C. D., OSTEN, O. L., MOIT, L. O., and STAHAN, M. S. Action of chemical and physical agents on the virus of equine infectious anemia, *Am. Jr. Vet. Res.*, 1944, *1*, 291.

## EDITORIAL

### METHODS OF ADMINISTERING PENICILLIN

THE inactivation of penicillin by the gastric juice, which renders it ordinarily ineffective by mouth, and its rapid excretion in the urine when given by parenteral injection, have given rise to troublesome technical difficulties in its administration. Thus far the most efficient method of maintaining an effective concentration in the blood and the most economical as far as the wastage of drug is concerned is the continuous intravenous drip. The practical disadvantages of this procedure are obvious and have stimulated many attempts to devise some simpler method of administration.

Subcutaneous injections are irritating and painful, and absorption has been reported to be irregular and uncertain.

After intramuscular injections absorption is rapid, reaching a maximum level which is highly effective after from 30 to 60 minutes, but it then falls off rapidly, and if ordinary doses are used (15,000 to 20,000 units), before the end of three hours the concentration often falls below the effective range. For susceptible organisms like the gonococcus, the pneumococcus and the hemolytic streptococcus, this is usually an effective procedure, although the necessity of continuing the injections day and night without interruption is a strain on the patient as well as the medical personnel. It is not adequate for the more resistant organisms such as the staphylococcus and the *Streptococcus viridans* in bacterial endocarditis.

Doubling the dose of penicillin injected prolongs somewhat the period during which an effective concentration in the blood is maintained, perhaps an hour. The alternatives are to reduce the interval to two hours, or to institute a continuous intramuscular drip. This can be done by dissolving the total daily dose of penicillin in 500 c c of salt solution and maintaining a flow at a rate of six to eight drops a minute. It maintains an effective concentration in the blood and is economical of penicillin. It is often painful; however, and is usually more objectionable to the patient than an intravenous drip, and except for freedom from thrombosis it shares most of the drawbacks of the latter procedure.

Attempts to improve the technic of intramuscular injections have been designed either to slow the rate of absorption or to lessen the rate of excretion in the urine.

In 1944 Raiziss<sup>1</sup> found that penicillin suspended in oil was more slowly absorbed and an effective concentration in the blood was maintained longer than when injected in aqueous solution. Romansky and Rittman<sup>2</sup> obtained

<sup>1</sup> RAIZISS, G. W. Penicillin in oil suspension. Bacteriostatic and spirocheticidal agent Science, 1944, c, 412-413.

<sup>2</sup> ROMANSKY, M. J., and RITTMAN, G. E. Penicillin prolonged action in beeswax-peanut oil mixture, single injection treatment of gonorrhea, Bull. U. S. Army Med. Dept., 1944 (Oct.), 43-49.

effective levels for six to 10 hours by injecting 100,000 units suspended in 3 per cent beeswax in peanut oil. They reported curing gonorrhea in a number of cases by a single injection.

Trumper and Hutter<sup>3</sup> utilized ice packs applied to the site of injection. In nine of 10 cases of gonorrheal infection they were able to maintain effective blood levels for six to 12 hours, and obtained clinical cure after a single injection of 50,000 or 100,000 units of penicillin. They usually applied the packs for two hours before the injection and for six or 12 hours following it.

Fiske, Foord and Alles<sup>4</sup> employed adrenalin to slow absorption. After demonstrating that penicillin was stable in dilute solutions of adrenalin and that in rabbits it prolonged the period during which an effective blood level was maintained after a single subcutaneous or intramuscular injection, they tested the mixture on seven human subjects. By dissolving 50,000 units of penicillin in 4 c.c. of 1-50,000 dilution of adrenalin solution, they approximately doubled the time during which an effective blood level (0.039 unit per c.c. or more) was maintained (about three hours as compared with one and one-half to two hours after injections of penicillin in salt solution).

Parkins et al.<sup>5</sup> attempted to combine these two principles by adding penicillin powder to a 6 per cent or 20 per cent gelatin solution containing 0.025 or 0.005 per cent of neosynephrine. In experiments on dogs and also in a few human cases they found that the use of either gelatin or neosynephrine prolonged the effect somewhat (to about four hours), but the use of both gave more satisfactory results. In human cases, following an intramuscular injection of 50,000 units, a significant blood level (0.02 to 0.08 unit per c.c.) persisted for six to eight hours. If this finding is confirmed, it should be possible in some cases to reduce the number of intramuscular injections per day from at least eight to three or four.

The early observation that high levels of penicillin were maintained in the blood for several hours in patients with renal insufficiency<sup>6</sup> led others to seek artificial means of slowing its excretion in the urine. Rammelkamp and Bradley<sup>7</sup> noted that excretion was delayed following diodrast injection. Beyer et al.<sup>8</sup> found that the addition of 6 per cent of sodium para-aminohippurate to penicillin solution on intravenous injection increased the plasma content of penicillin two to five times, depending upon the concentration of hippurate attained in the blood. No untoward effects were noted in short

<sup>3</sup> TRUMPER, M., and HUTTER, A. M. Prolonging effective penicillin action, *Science*, 1944, **6**, 432-434.

<sup>4</sup> FISKE, R. T., FOORD, A. G., and ALLES, G. Prolongation of penicillin activity by means of adrenalin, *Science*, 1945, **ci**, 124-125.

<sup>5</sup> PARKINS, W. M., et al. Maintenance of the blood level of penicillin after intramuscular injection, *Science*, 1945, **ci**, 203-205.

<sup>6</sup> RAMMELKAMP, C. H., and KEEF, C. S. Absorption, excretion and distribution of penicillin, *Jr. Clin. Invest.*, 1943, **xvii**, 425-437.

<sup>7</sup> RAMMELKAMP, C. H., and BRADLEY, S. E. Excretion of penicillin in man, *Proc. Soc. Exper. Biol. and Med.*, 1943, **liii**, 30-32.

<sup>8</sup> BEYER, K., et al. The effect of para-aminohippuric acid on plasma concentration of penicillin in man, *Jr. Am. Med. Assoc.*, 1944, **cxxvi**, 1097.

(12 hours) experiments in human cases. The hippurate is regarded as "competing" with the penicillin for excretion in the renal tubules.

Bronfenbrenner and Favour<sup>9</sup> studied the effect of administering benzoic acid by mouth (2.5 gm every four hours) on the rate of excretion and blood level of penicillin after intramuscular injections of 20,000 units. With a liberal fluid intake, this exerted only a moderate effect, but if at the same time fluid was restricted to 1000 to 1500 c.c. a day, and salt to 3 gm a day, the plasma concentration at 30 and 60 minute intervals was increased eight fold, and the duration of the high blood level prolonged to more than two hours.

Attempts have also been made to devise an effective procedure for oral administration. Penicillin is absorbed quite readily after it reaches the duodenum, but is inactivated by the acid gastric juice. It was noted early that in cases with achlorhydria, penicillin appeared in the blood after mouth administration. To protect the penicillin from this destructive action it has been administered in enteric coated capsules and in conjunction with various acid-neutralizing substances. The results obtained by the use of the ordinary enteric coatings have in general been inconstant and unsatisfactory.

Libby<sup>10</sup> suspended powdered sodium and calcium salts of penicillin in cottonseed oil and administered this in gelatin capsules. Following a single dose of 90,000 units the blood level ranged from 0.03 to 0.05 unit per c.c. for four hours. Two subsequent doses of 20,000 units at three hour intervals maintained this level for eight hours. The best results were obtained if the penicillin was given when the stomach was empty.

Charney et al.<sup>11</sup> administered 7 gm of trisodium citrate or 2.5 gm of disodium phosphate with penicillin by mouth, and determined the amount excreted in the urine during the subsequent six hour period as an index of absorption. When given after meals, there was on the average a substantial increase in the percentage of penicillin recovered in the urine as compared with the controls (from about 2 per cent to 20 per cent). The results with sodium bicarbonate, calcium carbonate and aluminum hydroxide in a few experiments were less satisfactory. When administered fasting, more penicillin was excreted by the controls and the increase obtained by the administration of the antacids was at best slight. Furthermore, individual variations were large.

McDermott et al.<sup>12</sup> followed the blood penicillin levels in a group of subjects after single oral doses of 315,000 units administered (1) in aqueous solution, (2) in aqueous solution preceded by three doses of 4 gm of magnesium trisilicate at one hour intervals, (3) in corn oil, and (4) in 4 per cent beeswax in peanut oil. Following this large dose, after 30 and 60

<sup>9</sup> BRONFENBRENNER, J., and FAVOUR, C. B. Increasing and prolonging blood penicillin concentrations following intramuscular administration, *Science*, 1945, ci, 673-674.

<sup>10</sup> LIBBY, R. L. Oral administration of penicillin in oil, *Science* 1945, ci, 178-180.

<sup>11</sup> CHARNEY, J., et al. Urinary excretion of penicillin in man after oral administration with gastric antacids, *Science*, 1945, ci, 251-253.

<sup>12</sup> McDERMOTT, W., et al. Oral penicillin, *Science*, 1945, ci, 228-229.

minute intervals, effective blood levels in the range of 0.6 to 0.8 unit per c.c. were recorded for all the procedures, without a significant difference between them, although the levels at the two hour interval were better sustained after the oil suspensions. They state that "qualitatively similar results" were obtained with doses of 100,000 and 50,000 units, and conclude that blood levels comparable to those following intramuscular injections can be obtained by oral administration of a dose five times as large.

Krantz, Evans and McAlpine<sup>13</sup> reported more successful results by the administration of 100,000 units combined with 3 gm. of basic aluminum aminoacetate. The average serum concentrations in 12 cases ranged from 0.39 unit per c.c. at two hours, 0.68 unit at three hours, 0.37 unit at five hours, to 0.17 unit at seven hours. There were large individual variations.

Burke et al.<sup>14</sup> also reported favorable results following the administration of penicillin in gelatin capsules hardened by immersion in formaldehyde and alcohol, 30 minutes after the ingestion of two tablets of aluminum hydroxide. These capsules resisted the action of gastric juice in vitro for one to two hours. Following 200,000 units, high blood levels were obtained after one-half hour and remained at an effective level for four to five hours. This level was maintained for about three hours after 100,000 units. This "compared favorably" with the average levels following 40,000 units intramuscularly.

Rectal administration has been regarded as impracticable because of destruction of penicillin by colon bacilli. Loewe et al.,<sup>15</sup> however, have obtained detectable concentrations in the blood of 12 of 14 cases following the administration of large doses (300,000 to 1,000,000 units) of sodium penicillin in cocoa butter suppositories. The results were variable, and in most cases the blood levels were low, but a level of at least 0.012 unit, the minimum effective against the most susceptible organisms, was maintained for six hours or more in half the cases tabulated. Manifestly the method must be greatly improved before it will have practical value.

Barach et al.<sup>16</sup> have reported promising results in the treatment of subacute and chronic infections of the lungs and bronchi by inhalations of penicillin aerosol. In these cases the concentration of penicillin in the blood usually ranged from 0.01 to 0.04 unit, and in one case to 0.18 unit, and could be increased by deep breathing to 0.4 unit. It seems quite possible that this may prove to be the best method of treating such conditions in which a high concentration of penicillin in the mucous membranes is presumably desirable. It seems unlikely that it would be practicable in other types of infection.

<sup>13</sup> KRANTZ, J. C., JR., EVANS, W. E., JR., and McALPINE, J. G. Oral penicillin with basic aluminum aminoacetate, *Science*, 1945, *ci*, 618-619.

<sup>14</sup> BURKE, F. G., ROSS, S., and STRAUSS, C. Oral administration of penicillin, *Jr. Am. Med. Assoc.*, 1945, *cxxxviii*, 83-87.

<sup>15</sup> LOEWE, L., et al. Penicillin by rectum, *Jr. Am. Med. Assoc.*, 1945, *cxxxviii*, 18-19.

<sup>16</sup> BARACH, A. L., et al. Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis, and lung abscess: preliminary report, *Ann. Int. Med.*, 1945, *xvii*, 485-500.

The reports which have been reviewed are all preliminary in nature, and the number of observations on which they are based is far too small to warrant any definite conclusions. Certain tentative ones, however, may be permissible.

Thus far no method except continuous intravenous or intramuscular drip can be depended upon to maintain continuously the relatively high blood concentration needed in infections with the more resistant organisms. Intramuscular injections of moderate doses of penicillin in aqueous solutions can not be depended upon to maintain a really effective blood level for more than two hours, although in many cases this may persist three hours. Doubling the dose of penicillin delays the fall in the blood level somewhat, but it is wasteful of drug, since a relatively large excess of penicillin is required to secure a comparatively slight delay. It is doubtful whether anything is gained from the transient excessively high levels reached soon after such injections.

It seems probable that some procedure designed to slow absorption may be so perfected that an adequate blood level can be maintained for at least eight hours after a single intramuscular injection. The most promising appear to be the use of oil or gelatin as a vehicle, in association with a persistent local vasoconstrictor. Procedures designed to retard excretion by the kidney require a great deal more study before their general use is justified.

The oral administration of penicillin is still in the early experimental stage, and at present it can not be depended upon in treating an infection of any gravity whatsoever. This preliminary work offers a definite hope that some effective procedure may be found, perhaps the use of an oil vehicle, a suitably hardened capsule, an effective antacid, or a combination of such measures. Thus far, however, it is little more than a hope. One point which stands out clearly is the great variability in the response of different individuals. Even those procedures which seem most promising on the basis of average values fail in certain cases. Large doses are required, at least two to five times that for intramuscular injection, and these would have to be repeated at least once in three or four hours to warrant any expectation of effectiveness. The indiscriminate dispensing of penicillin for oral use in combination with some antacid, which now threatens to come into vogue, is at present premature and ill advised, and is likely to prove highly disappointing.

Fortunately the primary toxicity of penicillin is negligible, and there is little risk of direct injury to the patient from such use. Penicillin also has much less tendency than the sulfonamides to render organisms resistant when it is administered intermittently and in inadequate doses. There is evidence, however, that certain individuals may become sensitized to penicillin. Cases of contact dermatitis have been reported, as well as generalized reactions during a second course of treatment.<sup>17</sup> The frequency of such reactions is not yet known, but this may prove an additional reason for avoiding the unnecessary or ineffectual administration of this drug.

<sup>17</sup> CRISP, L. H. Allergy to penicillin, *Jr. Am. Med. Assoc.*, 1944, **64**, 429.



## REVIEWS

*Radiologic Examination of the Small Intestine* By ROSS GOLDEN, M D 239 pages, 26 × 18 cm 1944 J B Lippincott, Philadelphia Price, \$6 00

The smallness of this book attests to the lack of knowledge of the diseases of the small bowel. It is apparent that this segment of the gastrointestinal tract has received less study than the remaining portions, which is perhaps due to its being more silent in its diseases than the rest. With the exception of complete obstruction of the small intestine, the symptoms produced by a pathological small bowel are far less dramatic than those of the stomach or colon.

On perusing this volume, it becomes evident that there is still much to be desired in roentgen examination of the small intestine. Dr. Golden presents very clear roentgenograms of the inflammatory, nutritional and emotional changes that occur in the small bowel. The immediate impression is that they are indistinguishable from one another.

The chemical mediator theory is discussed, together with case histories and the results of therapy based on this theory. But this, too, is still indefinite and calls for much further research.

The book is well illustrated and is very readable. The data included should act as a stimulus for further work on the small bowel. This volume could scarcely be classified as a reference one, since major portions of the information are inconclusive in nature.

D J B

*Savill's System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease for Students and Practitioners* Twelfth Edition. Edited by E C WARNER, M D, F R C P 1168 pages, 22 × 15.5 cm 1944 The Williams and Wilkins Company, Baltimore Price, \$9 00

The character of the present edition is unchanged from that of the first editions, which were planned by Dr. Thomas Savill and subsequently produced under the editorship of Dr. Agnes Savill. The changes are concerned mostly with modernization of methods of treatment and newer laboratory tests of established value. The greatest change has been in extracting "Psychological Disorders" from "Diseases of the Nervous System" and devoting a new chapter to this growing specialty.

The special value of this book is in its plan of organization, which is based on the presenting symptoms of disease. Each chapter is divided into three parts: (1) the symptoms the patient presents and the differential diagnosis, (2) the physical and clinical signs; and (3) a classification of diseases of that anatomical region with prognosis and treatment. Treatment is the weakest aspect of this edition, as it was in the previous ones. Some of this inadequacy may be due to the delays in publication during the rapid therapeutic advances of wartime. The sulfonamides are tabled briefly and the reader is cautioned against advising eggs, meat, and onions during their administration because of cyanosis due to sulf-hemoglobinemia and met-hemoglobinemia. Some of the inadequacy may be apparent rather than real and due to a difference in conventional therapeutic ideas in England and America, such as the value of morphine in asthma and of procedures of venesection and leeching in pneumonia with right heart strain; or, as in the case of "toxic adenoma (secondary Graves' disease)", the reader is advised against the use of iodine because it makes the condition worse.

The book is valuable to undergraduate and graduate clinicians who wish fundamental information in a readily available form. Symptoms which are classified in

other sections are described briefly and cross references are complete. It is because of this excellent organization that this book is superior to the usual text of differential diagnosis.

M V P

### BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*An Index of Differential Diagnosis of Main Symptoms* Sixth Edition. By Various Writers. Edited by HERBERT FRENCH, CVO, CBE, MA, MDOxon, FRCP. Assisted by ARTHUR H. DOUTHWAITE, MD, FRCP. 1128 pages, 26 × 17 cm. 1945. Williams and Wilkins Company, Baltimore. Price, \$17.00.

*Some Fundamental Principles of Metabolism*. By L. H. NEWBURGH, M. W. JOHNSTON, and J. D. NEWBURGH. 62 pages, 28 × 22 cm. 1945. J. W. Edwards, Ann Arbor, Michigan. Price: Paper bound \$1.25, cloth bound \$1.75.

*Text-Book of Pharmaceutical Chemistry* (Bentley and Driver). Fourth Edition. Revised by JOHN EDMUND DRIVER, MA (Cantab), PhD, MSc (Lond), FRIC. 644 pages, 22.5 × 14.5 cm. 1945. Oxford University Press, New York. Price, \$7.50.

*The Basis of Clinical Neurology*. Second Edition. By SAMUEL BROCK, MD. 393 pages, 23.5 × 16 cm. 1945. Williams and Wilkins Company, Baltimore. Price, \$5.50.

*Men Under Stress*. By ROY R. GRINKER, Lt Col, MC, and JOHN P. SPIEGEL, Major, MC, Army Air Forces. 484 pages, 24 × 16 cm. 1945. The Blakiston Company, Philadelphia. Price, \$5.00.

*The Bacterial Cell in Its Relation to Problems of Virulence, Immunity and Chemotherapy*. By RENÉ J. DUBOS. With an Addendum by C. F. ROBINOW. 460 pages, 22 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, \$5.00.

*A Synopsis of Medicine*. Eighth Edition. By SIR HENRY LETHBRIDGE TIDY, KBE, MA, MD, BCh (Oxon), FRCP (Lond). 1215 pages, 19 × 13 cm. 1945. Williams and Wilkins Company, Baltimore. Price, \$7.50.

*Common Ailments of Man*. Edited by MORRIS FISHBEIN, MD. 177 pages, 20.5 × 14 cm. 1945. Garden City Publishing Company, New York City. Price, \$1.00.

*Clinical Atlas of Blood Diseases*. Sixth Edition. By A. PINFEL, MD, MRCP, and STANLEY WYARD, MD, FRCP. 138 pages, 20.5 × 13.5 cm. 1945. The Blakiston Company, Philadelphia. Price, \$5.00.

# COLLEGE NEWS NOTES

## NEW LIFE MEMBERS

Since the publication of the last issue of the ANNALS OF INTERNAL MEDICINE, the following Fellows of the College have become Life Members (listed in the order of subscription)

Dr Hugo O Altnow, Minneapolis, Minn  
Dr Harold C Ochsnei, Indianapolis, Ind  
Dr Harry Plummer Ross, Richmond, Ind

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## ENLISTMENTS AND DISCHARGES, A C P MEMBERS

Dr Timothy F Breuer, F A C P, Hartford, Conn, has been commissioned a Lieutenant Commander in the U S Naval Reserve This brings the total number of College members who have entered upon military duty to 1,864

The following members of the College have been honorably discharged

Leroy E Burney, Senior Surgeon, USPHS—Indianapolis, Ind  
M Coleman Harris, Lieutenant Commander, (MC), USNR—New York, N Y  
Meredith B Hesdorffer, Past Assistant Surgeon, USPHS—Minneapolis, Minn  
Roy Herbert Holmes, Major, (MG), AUS—Muskegon, Mich  
W Byrd Hunter, Lieutenant Colonel, (MC), AUS—Huntington, W Va  
John L Kantor, Colonel, (MC), AUS—New York, N Y  
Charles H Watkins, Captain, (MC), USNR—Rochester, Minn

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## ORAL EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

Oral examinations by the American Board of Internal Medicine will be held in San Francisco, October 15-16-17 They are intended primarily for candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming The closing date for registering is September 1 Write for application form to the American Board of Internal Medicine, 1 West Main St, Madison 3, Wisconsin

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## GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged

### *Books*

"Rypins' Medical Licensure Examination," Fifth Enlarged Edition, completely revised under the editorial direction of Dr Walter L. Bierring, F A C P

### *Reprints*

Samuel M Alter, F A C P, Los Angeles, Calif—2 reprints  
Harold R Carter (Associate), Denver, Colo—2 reprints  
Irving Gray, F A C P, Brooklyn, N Y—5 reprints  
Harold J Harris, F A C P, Lieutenant Commander, (MC), USNR—3 reprints  
Franklin B Peck, F A C P, Indianapolis, Ind—1 reprint  
Bruce R Powers, F A C P, Knoxville, Tenn—1 reprint  
Horace K Richardson, F A C P, Baltimore, Md—1 reprint  
Mitchell A Spellberg (Associate) Major, (MC), AUS—7 reprints  
Leon H Warren, F A C P, Lieutenant Colonel, (MC), AUS—1 reprint

Office of The Surgeon General The local use of crystalline sulfonamides (sulfa powder) has therefore been discontinued except in the case of serous cavities where its use, while permissible under the direction of the surgeon, is not recommended This subject is covered by War Department Circular No 160 as amended by W D Circular No 176, 1945

*Colonel Lueth, Chief of Classification Branch*

Lieutenant Colonel Harold C Lueth, F A C P, of Evanston, Ill, has been assigned as Chief of the Classification Branch, Military Personnel Division, Office of The Surgeon General

Before coming to the Office of The Surgeon General in February of this year, Colonel Lueth was Liaison Officer for The Surgeon General to the American Medical Association, with headquarters in Chicago—a post which he held for three years He also served as Consultant in Procurement and Assignment to the War Manpower Commission

*Policy on Assignment of M C Officers to Veterans Administration*

Additional U S Army Medical Corps officers will not be assigned to duty with the Veterans Administration unless they had previously been serving on the staff of that organization, Major General George F Lull, F A C P, Deputy Surgeon General of the Army has announced

In outlining this War Department policy, General Lull stated that in the event officers specifically requested service with the Veterans Administration they would be eligible for such assignments

*Promotions in the Army Medical Corps*

From Lieutenant Colonel to Colonel

John Randall McBride (Associate), Hillsboro, Ohio

From Major to Lieutenant Colonel

Clifton Harold Berlinghof, F A C P, Binghamton, N Y

Sander Cohen, F A C P, Cincinnati, Ohio

Harold Ellsworth Hathhorn (Associate), Youngstown, Ohio

Samuel Edward King, F A C P, New York, N Y

Isadore Jacob Kwitny (Associate), Indianapolis, Ind

George William Stuppy, F A C P, Chicago, Ill

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Dr Leroy E Burney (Associate) has been given leave from the U S Public Health Service as of July 1, 1945, to assume the position of Secretary of the Indiana State Board of Health and State Health Commissioner of Indiana

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Colonel Orpheus J Bizzozero, F A C P, has been serving with the Army Medical Corps in Italy for a considerable period of time He will hold the Allied Military Government's health commission for the Milan region, it is announced He previously supervised medical services at Palermo and became Director of Public Health in Sicily He later served as a health officer in Rome and received an honorary degree in medicine from the University of Palermo

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The United States Public Health Service has recently issued the National Institute of Health Bulletin No 183 containing articles on typhus fever

Captain Lyle J Roberts, (MC), U S Navy, a Fellow of the American College of Physicians, was among medical officers taken prisoner by the Japanese in the Philippines in early 1942. It was not until May of 1945 that the College learned of that misfortune and found out through the wife of one of its other members, also a Japanese prisoner, that Captain Roberts was among the officers and men moved from the Philippines to some prison camp in Manchukuo.

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Dr Hugo T Engelhardt (Associate), for six years a member of the Department of Medicine at Tulane University School of Medicine, New Orleans, is now associated with the Humble Oil & Refining Company of Houston, Tex., as internist.

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Dr Charles F McKhann, F A C P, recently Assistant to the President in charge of research at Parke, Davis & Company, Detroit, has been named Professor of Pediatrics at Western Reserve University School of Medicine and Director of Pediatrics at the University Hospital, Cleveland. He succeeds Dr Henry J Gerstenberger, who will become Professor Emeritus of Pediatrics beginning with the next school year.

The appointment became effective as of July 1, but Dr John A Toomey, F A C P, will remain as Acting Director of Pediatrics at the University Hospitals until September 1. Dr Toomey will continue at Western Reserve University as Professor of Clinical Pediatrics and Contagious Diseases, and in charge of the Departments of Contagious Diseases at University and City Hospitals.

Dr McKhann is widely known for his work in pediatrics. He is a graduate of Miami University and holds the degree of Bachelor of Science, Master of Arts and Doctor of Medicine from the University of Cincinnati. He was assistant and instructor in the Harvard Medical School from 1923 to 1930, and Assistant Professor of Pediatrics and Communicable Diseases in the Medical School and the School of Public Health, Harvard University, from 1930 to 1936. From 1935 to 1940 he was Associate Professor at Harvard Medical School and its School of Public Health, and from 1940 to 1943 he was Professor of Pediatrics and Communicable Diseases at the University of Michigan. He was Visiting Professor of Pediatrics at Peiping Union Medical College, Peiping, China, from 1935-1936 on a grant from the Rockefeller Foundation.

In addition to his work as a teacher and administrator, Dr McKhann is probably best known for his work on the feeding of children and for his work with the fractionization of serums and the use of these serum fractions in the treatment of infectious diseases. He has contributed to several textbooks and is the author of more than fifty scientific papers.

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Dr John M Swan, F A C P, Rochester, N Y, is the Executive Secretary of the New York State Committee of the American Society for the Control of Cancer. He still holds a commission as Colonel in the Medical Reserve Corps (inactive) of the Army.

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#### FIFTY PER CENT INCREASE IN POLIOMYELITIS CASES

In the June issue of the National Foundation News it was reported that there is an increase of almost 50 per cent in the number of infantile paralysis cases for the first five months of 1945, as compared to the same period in 1944. A total of 740 cases was reported throughout the United States as of May 26 of this year. The greatest increase has been in the Middle Atlantic States where the number of poliomyelitis cases increased from 43 to 178. In the South Atlantic States there were 106 cases this year compared with 50 last year, the East South Central States, 79 this year, 32 last year, New England States increased from 15 to 30. West North Central

States increased from 30 to 41, East North Central States increased from 41 to 75, West South Central States increased from 110 to 122

A decrease occurred in the Pacific Coast States and the Mountain States

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#### ABBOTT LABORATORIES PROVIDE RESEARCH FOUNDATIONS

The Abbott Laboratories, North Chicago, Ill., recently announced an appropriation of \$50,000 for Research Fellowships in ten universities, \$5,000 each to support research in the field of medical products during a five-year period, beginning one year after the end of the war. The universities are given complete control of the results of the research conducted. Neither are they restricted regarding the type or scope of the problem selected within the specified field. Institutions selected include California Institute of Technology, Cornell University, Harvard University, University of Illinois College of Medicine, Massachusetts Institute of Technology, University of Minnesota, Ohio State University, Purdue University, Tulane University of Louisiana and the University of Wisconsin.

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#### LEGION OF MERIT AWARDS

##### Commodore William W Hargrave

Commodore William W Hargrave, F.A.C.P., (MC), U S Navy, formerly of Philadelphia, has been awarded the Legion of Merit, the citation reading "for exceptionally meritorious conduct in the performance of outstanding services to the government of the United States as medical officer in command of the United States Naval Hospital, Pearl Harbor, T H, from Aug 17, 1943 to July 3, 1944 and as medical officer in command of the United States Naval Hospital, Area, F H, from July 4, 1944 to Feb 9, 1945. A counsellor and director of rare understanding and broad vision, Commodore (then Captain) Hargrave exercised unfailing tact and wisdom in the administration of both hospitals and, applying his special knowledge with skill and judgment, created and maintained exceptionally high standards of professional service to the patients under his command. By his close personal supervision, his sympathetic concern and genuine interest in the individual welfare and morale of personnel, Commodore Hargrave inspired and encouraged the rapid rehabilitation of patients essential to the successful prosecution of the war against Japan."

##### Lieutenant Colonel Robert E Lyons, Jr

Lieutenant Colonel Robert E Lyons, Jr (Associate), (MC), AUS, formerly of Shreveport, La., was recently awarded the Legion of Merit for "Services as chief of the medical record division, Eighth Air Force, from July, 1942 to December, 1943. He devised methods of compiling wound and injury data from sick and wounded reports and field medical records which resulted in a complete medical record of Eighth Air Force combat wounds. The major portions of the body receiving wounds were indicated by percentages, representing a total of all wounds. This important record revealed that a large proportion of serious and fatal battle wounds among air crews was caused by relatively low velocity missiles incurred in an area of the body that could be protected by armor. Based on this study, individual armor equipment for the protection of air crew members was developed and standardized throughout the Eighth Air Force. By constant review of medical records, he continually developed new methods of presenting and interpreting statistical data. He charted the geographic incidence and sources of injuries and diseases which resulted in an immediate intensification of the venereal disease program in all areas. He utilized the material in the revised care of iller report to prepare charts and data which contributed greatly to

the reduction of frostbite and anoxia, thereby increasing the training level of combat crews before their shipment to the theater. He further conducted exhaustive research in the development of accurate attribution tables for air crews, of heavy bombardment units by reviewing the combat history of hundreds of crew members in each crew position throughout their entire combat careers. After an enormous amount of work and research he completed the report which served as a temporary basis for computing replacement requirements and proved invaluable to the Army Air Forces material and services commands. By his untiring efforts, competent grasp of the situation and high devotion to study he contributed materially to the outstanding success of the aerial offensive against the enemy."

#### Colonel Cornelius P Rhoads

Colonel Cornelius P Rhoads, F A C P, (MC), AUS, formerly of New York City, was awarded the Legion of Merit recently with the following citation "He developed new methods of diagnosis and treatment for relief of injuries due to toxic chemicals and perfected a compound to counteract the effects of blister gas. At Bushnell, Fla., and San Jose Island, Canal Zone, he established medical testing stations. He also developed equipment for detecting the presence of war gases in air, food and water."

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#### LIEUTENANT COLONEL ISIDORE A FEDER RECEIVES BRONZE STAR

Lieutenant Colonel Isidore A Feder (Associate), (MC), AUS, formerly of Brooklyn, recently received the Bronze Star "for meritorious service in connection with military operations against the enemy as Chief of Medical Service, 45th Evacuation Hospital, Semimobile, from June 17, 1944 to Aug 1, 1944 in France. Lieutenant Colonel Feder expertly supervised the diagnosis and treatment of numerous medical cases. He displayed keen insight in properly distributing the medical services of officers, nurses and enlisted personnel to insure prompt and adequate treatment of the wounded. By his initiative, professional knowledge and skill, Lieutenant Colonel Feder reflected credit on himself and on the military service."

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Dr Edward Kupka, F A C P, is Medical Director of the Hastings Foundation 101 Tuberculosis Research, Pasadena, Calif

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Dr George C Lockard, F A C P, will represent the University of Maryland School of Medicine, Dr Robert H Riley, F A C P, will represent the State Department of Health, and Dr Victor F Cullen, F A C P, will represent the Maryland State tuberculosis sanatoriums, on the newly created Council on Medical Care set up by authority vested in the State Board of Health in Maryland to provide consultation and advice in connection with the program to be administered by the Bureau of Medical Services of that State.

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Dr George K Wharton, F A C P, Kingston, Ont., is now Professor of Clinical Medicine at Queens University, Chief of the Clinical Service on Medicine at Kingston General Hospital and Consultant in Medicine at Hotel Dieu. He is certified by the American Board of Internal Medicine and by the Specialty Board of the Royal College of Physicians and Surgeons of Canada.

Dr John F Kenney, F A C P, Pawtucket, has been installed as President of the Rhode Island Medical Society

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Dr Waller S Leathers, F A C P, retired on June 30, 1945, as Dean of Vanderbilt University School of Medicine, Nashville Dr Leathers had served as Dean and Head of the Department of Preventive Medicine and Public Health since 1928 He was succeeded by Dr Ernest W Goodpasture who heretofore had been Associate Dean and Professor of Pathology

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Dr Edwin J Simons, F A C P, Swanville, has been elected President of the Minnesota State Medical Association and succeeds Dr Edward L. Tuohy, F A C P, Duluth, on January 1, 1946 Dr Benjamin B Souster, F A C P, St Paul, was elected Secretary

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#### AMERICAN BOARD OF PEDIATRICS TO HOLD EXAMINATIONS

The American Board of Pediatrics will conduct its oral examination at Atlantic City, N J, Hotel Claridge, December 7-9 The examination was first scheduled for New York City, but had to be changed because hotel reservations were not available The written examination of the Board will be conducted locally under a monitor on October 19

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Dr Andrew C Ivy, F A C P, will supervise the work of research in cancer education at Northwestern University, Chicago, under a grant in aid of \$8,500 by the National Advisory Cancer Council Dr James H Means, F A C P, will likewise supervise the study of the relation of steroid hormones to growth and tumors under a grant of \$24,500 to Harvard University from the same source Dr Leon Schiff, F A C P, will supervise clinical studies of gastric cancer under a grant of \$10,000 from the Council to the University of Cincinnati The total grant to all institutions by the National Advisory Cancer Council is \$79,377, the largest amount ever granted at one time by the Council

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Dr Virgil P Sydenstricker, F A C P, Professor of Medicine at the University of Georgia School of Medicine, Augusta, is now Chief of the United Nations Relief and Rehabilitation Association's Nutrition Service and is reported still to be aiding patients at the Belsen Concentration Camp in Germany

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#### Correction

Dr. Paul R Meyer, Port Arthur, Tex, was honorably discharged from the Army Air Corps as a Lieutenant Colonel rather than as a Captain, is published in the June issue of this journal

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On June 23, 1945, the University of Southern California conferred the honorary degree of Doctor of Science upon Walter L Treadway, M D, F A C P, formerly Assistant Surgeon General (1929-38) and Medical Director (Retired), United States Public Health Service



## THE WAR-TIME GRADUATE MEDICAL MEETINGS

The more active program of the War-Time Graduate Medical Meetings is somewhat suspended during the summer months although this period is used in preparing and organizing the sessions for the early autumn

Under the chairmanship of Dr James J Waring, F A C P, Denver, Zone No 19, a program was given at the hospital at Camp Carson, Colorado Springs on July 19 including "Surgery of the Sympathetic Nervous System," Dr Merrill C Jobe, "Pulmonary Infarction," Dr R W Vines, "Recent Advances in Diabetes," Dr S S Kauvar, F A C P

In Zone No 23 a graduate medical meeting will be conducted at the Dibble General Hospital, Menlo Park, California on September 3 including "Diagnosis and Treatment of Arthritis," Dr S R Mettier, F A C P, "Nephritis," Dr Leslie L Bennett

A review of the activities of the committee for the six months ending June 30, 1945 reveals that over the country there have been 60 individual meetings of 111 sessions and 90 continuation courses of 646 sessions, making a total of 150 meetings and 757 total sessions. These were conducted in 101 army installations, 23 naval installations and 7 at civilian centers. The total cost for this rather extensive program including administration, printing, traveling expenses of the committee and instructors, honoraria to instructors in certain instances and other miscellaneous items amounted to \$14,119.01

Inquiries are received at the executive offices of the committee from time to time from entirely new installations where programs have not been previously conducted. There has been a steady recognition and growing appreciation of the value of this nation-wide effort among the medical officers of our armed forces

## TEN FELLOWSHIPS IN PSYCHIATRY AVAILABLE AT UNIVERSITY OF MICHIGAN

There are now ten one-year fellowships in Psychiatry available at the University of Michigan. Each will offer an annual stipend of \$2,000. These fellowships are under the aegis of the Office of Veteran's Affairs of the State of Michigan. Appointees will be trained at the Neuropsychiatric Institute of the University of Michigan. Candidates must be graduates of a Class A Medical School, and must complete a rotating internship before beginning their fellowship. Applications should be made to Dr Raymond Waggoner, Professor of Psychiatry, University Hospital, Ann Arbor, Michigan

## MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa

June 10, 1945

The regular spring meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters, Philadelphia, June 10, 1945, with President Ernest E Irons presiding, Mr E R Loveland acting as Secretary, and the following in attendance

|                       |                       |
|-----------------------|-----------------------|
| ERNEST E IRONS        | President             |
| WALTER W PALMER       | First Vice President  |
| JAMES J WARING        | Second Vice President |
| WILLIAM D STROUD      | Treasurer             |
| GEORGE MORRIS PILLSOL | Secretary-General     |

JONATHAN C MEAKINS  
 HUGH J MORGAN  
 CHARLES F TENNEY  
 FRANCIS G BLAKE  
 ROGER I LEE  
 CHARLES T STONE  
 JAMES E PAULLIN  
 LEROY H SLOAN  
 MAURICE C PINCOFFS  
 PAUL W CLOUGH  
 CHAUNCEY W DOWDEN  
 O H PERRY PEPPER

Editor, ANNALS OF INTERNAL MEDICINE  
 Acting Editor, ANNALS OF INTERNAL MEDICINE  
 Chairman, Board of Governors  
 Chairman, Committee on Finance

The Executive Secretary read abstracted Minutes of the preceding meeting of the Board, which were approved as read

The Executive Secretary, among the communications, presented the resignation of Dr Fred W Wilkerson, F A C P, Montgomery, Governor of the College for Alabama, the resignation being submitted because of illness. President Irons, after consulting the Board, appointed Dr E Dice Lineberry, F A C P, Birmingham, as Governor for Alabama to fill out the unexpired term of Dr Wilkerson, namely, until 1947.

President Irons announced the sudden death of Dr William W Herrick, F A C P, New York, N Y, on June 1. Dr Herrick had been serving as the member of the Committee on Post-War Planning for Medical Service, and at one time had served as a Regent of the College. President Irons announced the appointment of Dr Walter W Palmer, F A C P, New York, N Y, to succeed Dr Herrick on the Committee on Post-War Planning for Medical Service.

As a communication, Mr Loveland reported that due to illness, Dr Sydney R Miller, F A C P, Baltimore, resigned some months ago as a member of the Committee on Credentials, and the appointment subsequently by President Irons of Dr LeRoy H Sloan, F A C P, Chicago, succeeding Dr Miller for a term expiring in 1945 or until the next date when appointments are made.

It was suggested by Dr James E Paullin that the President send a letter of thanks to Dr Wilkerson and to Dr Miller for their valuable service to the College.

The Secretary-General, Dr George Morris Piersol, reported the deaths of 34 Fellows and 3 Associates since the last meeting of the Board, as follows

#### *Fellows*

|                        |                     |                   |
|------------------------|---------------------|-------------------|
| *Clendenning, Logan    | Kansas City, Mo     | January 31, 1945  |
| Contair, William Freas | Benton, Pa          | January 11, 1945  |
| Cotter, Thomas F       | Indiana Harbor, Ind | March 12, 1945    |
| Dever, Francis Joseph  | Bethlehem, Pa       | December 30, 1944 |
| Dibble, John           | MC, U S Army        | April, 1943       |
| Donald, William M      | Detroit, Mich       | December 20, 1944 |
| Flinn, John W          | Prescott, Ariz      | November 21, 1944 |
| Gorham, Frank D        | St Louis, Mo        | November 27, 1944 |
| Grant, Brooks Collins  | MC, U S Army        | January 1, 1945   |
| Grauer, Frank          | New York, N Y       | February 16, 1945 |
| Grill, John C          | Milwaukee, Wis      | March 17, 1945    |
| Hall, William W        | Watertown, N Y      | January 3, 1945   |
| *Herrick, William W    | New York, N Y       | June 1, 1945      |
| Irving, Peter          | New York, N Y       | December 28, 1944 |
| Klaus, Emanuel         | Cleveland Ohio      | March 21, 1945    |
| Klopp, Henry Frank     | Allentown Pa        | March 7, 1945     |

\* Former Regents

|                           |                    |                   |
|---------------------------|--------------------|-------------------|
| Lawrence, Charles H       | Boston, Mass       | March 13, 1945    |
| Luippold, Eugene John     | Weehawken, N J     | December 16, 1944 |
| Mahony, Fergus O          | El Dorado, Ark     | February 6, 1945  |
| Mills, Harlan Page        | Phoenix, Ariz      | February 27, 1945 |
| Neal, Frank               | Peterborough, Ont  | January 18, 1945  |
| Nicholas, Estes           | Portland, Maine    | December 12, 1944 |
| Northrup, William         | Ionia, Mich        | December 9, 1944  |
| Pepper, John K            | Winston-Salem, N C | October 31, 1944  |
| Pudor, Gustav A           | Portland, Maine    | March 7, 1945     |
| Purdie, Robert McNair     | Houston, Tex       | April 9, 1945     |
| Ricketts, George Allen    | Osceola Mills, Pa  | December 6, 1944  |
| Rudy, Abraham             | Boston, Mass       | February 19, 1945 |
| Sinclair, Charles George  | M C, U S Army      | May 3, 1945       |
| Smith, Bertnard           | Los Angeles, Calif | January 23, 1945  |
| Speidel, Frederick George | Louisville, Ky     | October 15, 1944  |
| Warren, Mortimer          | Portland, Maine    | October 8, 1944   |
| Weissberg, Morris         | Brooklyn, N Y      | March 17, 1945    |
| Winemiller, James Lewis   | Great Neck, N Y    | October 1, 1944   |

*Associates*

|                   |                    |                   |
|-------------------|--------------------|-------------------|
| Smith, Esmonde B  | Brooklyn, N Y      | February 2, 1945  |
| Talbot, Francis J | Niagara Falls, N Y | November 11, 1944 |
| Willett, Thomas   | West Allis, Wis    | February 25, 1945 |

Dr Piersol reported the following list of 65 additional Life Members since the last meeting of the Board, making a grand total of 387 Life Members, of whom 33 are now deceased, leaving a balance of 354 (named in the order of subscription)

|                        |                         |
|------------------------|-------------------------|
| Albert F R Andresen    | Brooklyn, N Y           |
| Henry A Christian      | Brookline, Mass         |
| Erwin D Funk           | Wyomissing, Pa          |
| George M Levitas       | Westwood, N J           |
| Eugene E Marcovici     | New York, N Y           |
| Samuel T Nicholson, Jr | Pottstown, Pa           |
| Ralph L Shanno         | Forty Fort, Pa          |
| Carl Edward Johnson    | Morgantown, W Va        |
| Frank B Kelly          | Chicago, Ill            |
| David L Perry          | New Castle, Pa          |
| Fred John McEwen       | Wichita, Kan            |
| John W Scott           | Lexington, Ky           |
| V M Longmire           | Temple, Tex             |
| Irving J Sands         | Brooklyn, N Y           |
| John Albert Bauer      | Burlington, Ont, Canada |
| William S Reveno       | Detroit, Mich           |
| Irvin R Fox            | Eugene, Ore             |
| Joseph Kopecky         | San Antonio, Tex        |
| Randolph Lyons         | New Orleans, La         |
| Robert G McCorkle      | San Antonio, Tex        |
| Thomas P Sprunt        | Baltimore, Md           |
| Meldrum K Wylder       | Albuquerque, N M        |
| Joseph A Pollia        | Los Angeles, Calif      |
| Fred Sternagel         | West Des Moines, Iowa   |
| C Clyde Sutter         | Rochester, N Y          |
| Chester Quay Thompson  | Omaha, Nebr             |

|                          |                       |
|--------------------------|-----------------------|
| Arthur Christian DeGraff | New York, N Y         |
| John Day Garvin          | Pittsburgh, Pa        |
| John E Nelson            | Seattle, Wash         |
| D D Comstock             | Los Angeles, Calif    |
| W Bernard Yegge          | Denver, Colo          |
| Elliott P Smart          | Murphys, Calif        |
| Guy D Callaway           | Springfield, Mo       |
| Thomas Everett Strain    | Shreveport, La        |
| Francis M Pottenger, Jr  | Monrovia, Calif       |
| Clarence C Campman       | West Middlesex, Pa    |
| G Stirling Landon        | San Bernardino, Calif |
| Roy A Ouer               | San Diego, Calif      |
| John H Fitzgibbon        | Portland, Ore         |
| Henry M Ray              | Pittsburgh, Pa        |
| Samuel Gitlow            | New York, N Y         |
| Sigurd W Johnsen         | Passaic, N J          |
| Franklin Jesse Nelson    | Tulsa, Okla           |
| Homer A Ruprecht         | Tulsa, Okla           |
| George R Maxwell         | Morgantown, W Va      |
| Henry Nelson Tihen       | Wichita, Kan          |
| Jacob M Cahan            | Philadelphia, Pa      |
| Irving L Cabot           | Brooklyn, N Y         |
| Harold F Koppe           | Dayton, Ohio          |
| Harvey M Ewing           | Montclair, N J        |
| Homer D Cassel           | Dayton, Ohio          |
| Otto A G Reinhard        | Lincoln, Nebr         |
| Charles H Parsons        | Concord, N H          |
| Lawton M Hartman         | York, Pa              |
| Leopold Shumacker        | Chattanooga, Tenn     |
| Anita M Muhl             | San Diego, Calif      |
| Donald R McKay           | Buffalo, N Y          |
| Wm Lindsay Miller        | Gadsden, Ala          |
| Samuel G Shepherd        | Philadelphia, Pa      |
| William D Stroud         | Philadelphia, Pa      |
| Vernon L Evans           | Aurora, Ill           |
| Frank Baker Marsh        | Salisbury, N C        |
| Harry Joseph Friedman    | Seattle, Wash         |
| Mark Alexander Griffin   | Asheville, N C        |
| William Ray Griffin      | Asheville, N C        |

The report of the Secretary-General was unanimously adopted

Dr George Morris Piersol, as Chairman of the Committee on Credentials, then presented the following report

"Since the last meeting of the Board of Regents, Dr Sydney R Miller, for many years a member of this Committee, resigned, and Dr LeRoy H Sloan was appointed by the President to fill his unexpired term

"The Committee met yesterday with all members present

"The Committee unanimously recommends to the Board of Regents the reinstatement of Commander Charles Leroy Denton, Dyersburg, Tenn, to Associateship. Dr Denton is entitled to a period of ten months more as an Associate following his retirement from active naval service during which to qualify for Fellowship. The Committee also recommends the reinstatement to Fellowship of Dr Claude L Holland, Fairmont, W Va; Dr Holland resigned a few years ago because of ill health

and other problems His application for reinstatement is accompanied by check to cover past dues He had been a Fellow for many years"

On motion by Dr Paullin, seconded by Dr Palmer, and regularly carried, the above portion of the report of the Committee on Credentials was approved

DR PIERSON (continuing) The Committee reviewed the credentials of 150 candidates for Fellowship Copies of the full list have been distributed to the Board The summary of the Committee's recommendations are as follows

|   |       |
|---|-------|
| Recommended for Advancement to Fellowship       | 78    |
| Recommended for Election to Direct Fellowship   | 23    |
| Recommended for Election First to Associateship | 9     |
| Deferred for Further Credentials                | 29    |
| Rejected  | 11    |
|   | <hr/> |
|   | 150   |
|   | <hr/> |

On motion by Dr Piersol, seconded and regularly carried, the following list of 101 candidates were elected to Fellowship (This list was published in the July issue of this journal)

DR PIERSON (continuing) The Committee reviewed the credentials of 156 candidates for Associateship, and a summary of its recommendations is as follows

|   |       |
|---|-------|
| Recommended for Election to Associateship | 99    |
| Deferred                                  | 29    |
| Rejected                                  | 28    |
|   | <hr/> |
|   | 156   |
|   | <hr/> |

To this number must be added the 9 candidates for direct election who are recommended for election first to Associateship, making a total number of recommendations for election to Associateship of 108

On motion by Dr Piersol, seconded by Dr Palmer, and regularly carried, the following 108 candidates were elected to Associateship (This list was published in the July issue of this journal)

DR PIERSON (continuing) The Committee makes the following report on the class of Associates elected five years ago, March 31, 1940

|                                       |       |
|---------------------------------------|-------|
| Qualified and Advanced to Fellowship  | 100   |
| Deceased                              | 2     |
| Deferred, because of Military Service | 32    |
| Dropped, Failed to Qualify            | 10    |
|                                       | <hr/> |
|                                       | 144   |
|                                       | <hr/> |

Five Associates who are practicing physicians have failed to qualify for Fellowship within the five-year maximum term, and in accordance with regulations of the Board of Regents and the By-Laws are recorded as dropped from the Roster Thirty-three Associates have been granted an extension of time, because of active military service, to qualify for Fellowship following discharge

Dr Chauncey W Dowden, Chairman of the Board of Governors, brought to the attention of the Committee reports and suggestions from the majority of the Governors of the College These suggestions were discussed at length, especially from the standpoint of the recommendation of the Board of Regents that certification shall

some time in the future become a prerequisite for election to Associateship. A resolution was adopted by the Committee on Credentials to recommend to the Board of Regents the following plan

- (1) Certification shall be a prerequisite for Associateship,
- (2) If this rule is adopted, the College shall abandon the five-year maximum Associate term, which will require amendments to the By-Laws,
- (3) The specific qualifications for Fellowship shall be revised by the Credentials Committee, subject to approval by the Board of Regents,
- (4) The present rules for direct election to Fellowship in special cases shall be retained,
- (5) These changes shall become effective as of the date of adoption, and shall apply to all Associates on the Roster at that time, provided they have become certified, other Associates not certified shall remain in the Associate status,
- (6) The Committee is cognizant of the effect these changes will have on the age of physicians on admission to the College and the effect also on the post-graduate course program

Because the last recommendations were subject to discussion, Dr Piersol moved that the balance of the report of the Committee on Credentials, exclusive of the last recommendations, be adopted

The motion was seconded by Dr Waring and passed

It was moved by Dr Piersol, seconded by Dr Lee that the Board of Regents adopt the new recommendations, constituting the latter part of the report of the Committee on Credentials regarding revised requirements for membership. The matter was opened for discussion

**PRESIDENT IRONS** There are manifestly certain advantages in the recommendation of the Credentials Committee. There are one or two disadvantages. The first is, in the view of the Chair, that if you take this action you are making a gate for the membership through which members enter the College and delegating the function of gatekeeper to the Board on Internal Medicine, which is separate from the College. It is true the Board works in close harmony with the College, but it is an outside organization, and I doubt the wisdom or the constitutionality of delegating to an outside body who shall be elected a member of the College. Secondly, there is another educational objection. The five-year Associate term is a period during which the young man gets, or should get, the stimulus of College association. His Associateship is one of the things that helps him on his way. The American Board has stimulated progress and education among younger men. The whole attitude of the young man after he leaves his hospital has been changed in many cases. The Associate period or probation is a period of stimulation, during which the young man is likely to be helped to grow by his College associations. If you say to him, "You cannot even look in at the door until after you have been certified," then you take away from him one of the aids that he would have had in accomplishing his passage of his Board examinations. These two objections should be very seriously considered, notwithstanding the fact that there are cogent other reasons submitted in favor of the motion by the Credentials Committee. We ought to have very careful discussion of this matter, because it is fundamental.

**DR ROGER I. LEE** Mr President, a good many of us are more accustomed to studying things from the printed word than we are from the spoken word. We have had this report read to us. It is very important. It is worthy of most careful consideration, and I myself should doubt very much whether action should be taken at this time. I should like, therefore, to move that this be written up and circularized

now and before the next meeting of this Board, in order to give us plenty of opportunity to study and reflect upon these very fundamental changes

The previous motion was withdrawn, and Dr Lee's motion substituted It was seconded by Dr Waring and adopted

Dr Roger I Lee, Chairman of the Committee on Public Relations, presented the following report

"The Committee met on June 9, 1945, at 11 00 a m , at the College Headquarters Those present were Drs Paullin, Irons and Lee

#### I *Resignations*

The Committee voted to recommend the acceptance of the resignation of Dr Leon Ashman (Associate), Baltimore, Md ,

Recommended the retention on the Roster of Fellows the name of Dr Herbert L Reynolds, F A C P , Atlanta, Ga , with waiver of dues until his recovery and resumption of practice ,

Recommended the acceptance of the resignation of Dr Harry Perry Thomas (Associate), San Antonio, Tex

#### II *Fees and Dues Cases*

The Committee voted to recommend the waiving of dues on account of illness, until recovery and resumption of work, in the case of one Associate and three Fellows

#### III *Communications*

Certain communications were received and read It was voted to recommend the reference to the American Heart Association of the communication of Dr L R McCauley, F A C P , re coronary deaths among physicians ,

- It was voted to recommend the filing of a resolution by Veterans Affairs Committee of Brooklyn, N Y , and the filing with thanks of communications from the British Consulate General re Rehabilitation Films and from the National Research Council

#### IV *Delinquent Members*

It was voted that in accordance with provisions of the By-Laws of the College five delinquent members be informed that their names must be dropped from the Roster unless their dues accounts are brought up to date within a period of sixty days herefrom

On motion by Dr Lee, seconded and regularly carried, the recommendations of the Committee were adopted, and the report as a whole was approved

Dr Walter W Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported a meeting by that Committee on June 9, with all members of that Committee present, and with Dr David P Barr sitting in on the deliberations of the Committee He brought certain facts, furnished by the Executive Secretary, to the attention of the Board, including the 1936 circulation of the journal was 3,627, whereas it is now in excess of 7,400, the College has lost through reduction in Initiation Fees and the waiving of dues of members on active military service something in excess of \$25,000 00 annually, the income of the College has been considerably increased through subscriptions to the journal, for instance, the circulation in December, 1941, at the opening of the War, was 5,505, and the circulation for May, 1945, was 7,412, an increase of 1,907 or 34 6%, the advertising income for 1941 was \$9,096 12 and for 1944, \$13,279 83, an increase of \$4,183 71 or 45 9%, the advertising income for 1945 will be materially further increased, increase in circulation has been due, in the opinion of the Committee to the improvement in the quality of the journal increases in the advertising rates will go into effect as of July 1, 1945, the cost of publication has increased through the years as follows

## Cost per page—

|             |        |
|-------------|--------|
| May, 1936   | \$7 13 |
| May, 1938   | 7 48   |
| May, 1940   | 7 69   |
| May, 1942   | 8 22   |
| May, 1944   | 9 18   |
| April, 1945 | 9 84,  |

an increase since 1936 of \$2.71 per page. The journal is due to come from press about the sixteenth of each month, but the printers have had labor shortage, and the delay has been largely due to the printers, rather than the Editor's Office. An effort will be made to improve this situation. The Committee believed that if the Editor could publish during the year four or five fairly comprehensive good reviews and offer sufficient honoraria for the reviews, the value of the journal would be enhanced. To that end, the Committee recommended that the Editor be authorized to offer an honorarium of \$100.00 for each such review, not exceeding five reviews per year.

In closing his report, Dr. Palmer said: "The Committee is impressed with the work of the Editor and the Executive Secretary, and wish to express their keen appreciation."

President Irons called upon the Editor, Dr. Paul W. Clough, for a report.

DR. PAUL W. CLOUGH: I have little to add. We have gotten the *ANNALS* out without any undue difficulty. The same problems that have been discussed previously are still present—the question of suitable material. The size of the journal has been reduced a little. The current Volume, which will be concluded with the June number, will probably be about one hundred pages shorter than the Volume of a year ago. Material is coming in a little better at the present time, and the quality is a bit better. We have at present enough material in the way of main articles to complete the November number, and somewhat more than enough case reports already accepted to complete that number. In other words, we are publishing about six months after the receipt of manuscripts. Articles which are of active interest and which it is desirable to get into print promptly, usually can be published in about three months. The actual mechanics of getting an article into print following submission of the manuscript to the printer requires about two months. The delay in the appearance of the journal at present is largely due to the printer's difficulties. Manuscripts and Editorials have gone in promptly. Our major deficiency right now is getting adequate book reviews. Some of the members of the Board have helped us out at times in finding reviewers of certain books, but personally I have practically no time to devote to that, and it has been extremely difficult to find competent reviewers.

DR. O. H. PERRY PEPPER: President Truman yesterday appointed a board to declassify secret material in the scientific and technical fields. That may lead to the freeing of a quantity of very excellent work, and it would seem desirable if the *ANNALS* were to clear its decks, so to speak, for two reasons: first, this material would be new and valuable; secondly, it would be of great service to these men who have done this work and have been prevented from receiving their proper recognition.

On motion seconded and regularly carried, the Editor's report was accepted.

At this point, President Irons asked Colonel Maurice C. Pincoffs to make some remarks.

COLONEL MAURICE C. PINCOFFS: Mr. President, I can only say that the *ANNALS* have been coming over to our theater and neighboring theaters with reasonable regularity, and these journals (and I include other outstanding clinical journals) have meant a tremendous lot to the men in the smaller hospitals and other medical institutions in the theater. When I left Baltimore I thought the *ANNALS* would have a



very difficult time as the War went on in finding suitable material, but it seems to me that it has improved rather than retrogressed in any way. I think the motion of thanks to the Acting Editor is certainly fully deserved.

President Irons then called upon Dr. Piersol to present a report on the War-Time Graduate Medical Meetings Committee.

Dr. Piersol, on behalf of the Chairman, Dr. Francis F. Borzell, presented a brief report of the activities of the War-Time Graduate Medical Meetings Committee, emphasizing the continuance of its active program. He also presented a financial report for the period January 1 through May 31, 1945, showing receipts amounting to \$23,747.85, represented in contributions by the American College of Physicians, the American College of Surgeons and the American Medical Association, and expenditures of \$11,550.63, with a cash balance on May 31, 1945, of \$12,197.22. The largest single expenditure for the War-Time Graduate Medical Meetings is the traveling expense account of instructors.

DR. ROGER I. LEE: This Committee has done a very outstanding job, and it deserves the grateful thanks of everybody. It has worked hard and toiled many times with the greatest of difficulties, and I don't want to be too eulogistic, but it would be too bad if there were not something said of earnest praise for its work. I move that the thanks of the Regents be forwarded to the Chairman and the Committee.

The motion was put and unanimously carried.

President Irons called upon Dr. Francis G. Blake to report for the Committee on Fellowships and Awards.

DR. FRANCIS G. BLAKE: The Committee on Fellowships and Awards met on June 9, with Drs. Fitz, Meakins and the Chairman present. The Committee thinks there will be suitable candidates for Research Fellowships during 1946, perhaps both from men being discharged from the Armed Forces and from the usual other sources. The Committee, therefore, presents the recommendation that the American College of Physicians' Research Fellowships be reestablished in 1946, that \$7,500.00 be appropriated for these fellowships, and that the Executive Committee be authorized to make interim appointments on the recommendation of the Committee on Fellowships and Awards. The Committee feels there should be a little more leeway with respect to stipends, particularly in the case of applicants who may be discharged from the Armed Forces, and it recommends that Research Fellowships may range from \$1,800.00 to as much as \$2,500.00. The reason for suggesting interim appointments bears on the possibility of applications being received from men discharged from the Armed Forces at unstated times during the course of the year. It would seem unfortunate if there had to be a long interim until the next meeting of the Board of Regents for the awarding of Research Fellowships in such cases. If such authority is granted to the Executive Committee, such an interim may be avoided.

The adoption of this recommendation was moved by Dr. Blake, seconded by Dr. Paullin and carried.

DR. BLAKE (continuing): The Committee considered the John Phillips Memorial Award, and recommends that it be reestablished at such time as the College may hold its next Annual Meeting.

On motion by Dr. Blake, seconded by Dr. Lee, this recommendation was approved.

DR. BLAKE (continuing): The Committee recommends that \$25,000.00 be appropriated for 1946 for Clinical Fellowships in Internal Medicine, available for Fellows and Associates and prospective candidates for Associateship honorably discharged from the Armed Forces, that these fellowships be limited to a term of one year, and shall not be renewable, that the Executive Committee be authorized to make interim appointments on the recommendation of the Committee on Fellowships and Awards. These Clinical Fellowships should be established in Internal Medicine, organized by

the College for the assistance of men coming out of the Armed Forces. There are a great many of them who at the present time have indicated they would like either one or two years' training experience in Internal Medicine. Many indicated they would like three months, six months, or nine months of training. The Committee realizes that any such undertaking would probably interest particularly the younger group of officers who might be considered as potential candidates for Associateship, but in addition to that, if College money is to be used for this purpose, it also should be available for Associates, if there is an occasional Associate who would like to take advantage of it—also any Fellow, although it is not thought by the Committee there will be many applicants from that group. It is realized that this will require a fair amount of money, which probably could not be appropriated from current income, but would have to be considered as a sum to be appropriated from capital funds.

It was also suggested by the Committee that the Officers of the College might possibly consider this a nucleus contribution from the College and might approach the Foundations to see whether they would be willing to match this amount for this purpose. I move the adoption of the recommendations.

**PRESIDENT IRONS** A matter of similar character will come up in the report of the Committee on Post-War Planning for Medical Service. It would be appropriate to discuss the two together, and to accept your motion and to take a later vote on it, after discussion of a forthcoming report.

**DR BLAKE** That will be acceptable to the Committee. I move then the acceptance of the report as a whole, excluding the last recommendation until further vote is taken.

The motion was seconded by Dr Paullin and unanimously carried.

President Irons called upon the Chairman of the Board of Governors, Dr Chauncey W Dowden.

Dr Dowden reported that he had circularized the Governors, asking for expressions of opinion upon the question of certification as a prerequisite for Associateship, the tenure of office for Governors, membership credit for candidates who have had special training while in Service, and post-war activities of the College. He suggested that he and/or the Executive Secretary obtain enough copies of the American Board of Internal Medicine literature concerning purposes, regulations, etc., to distribute to every member of the Board of Governors. He proposed to send a communication to the Governors again, asking them to study more in detail the regulations of the American Board of Internal Medicine, so that they can discuss the whole matter of certification more intelligently when they are permitted next to have a meeting.

Dr James J Waring presented a report on the American Board of Internal Medicine in the absence of the Chairman, Dr Reginald Fitz. The report revealed the Board has a surplus of approximately \$51,000.00. The Board has already reduced the examination fees and has reduced its expenditures. Guest examiners are given a small honorarium. The Board may consider further reduction in the fees in the future, because it wants to maintain only a respectable and safe reserve.

President Irons reminded the Board that the American College of Physicians needs to make two appointments to the Board. Dr William S. McCann, F.A.C.P., Rochester, N. Y., was nominated and elected a member of the Board for term expiring 1947, filling the unexpired term of Dr Frederic M. Hanes, F.A.C.P., Durham, N. C., resigned. Dr Truman G. Schindler, F.A.C.P., Philadelphia, Pa., was nominated and elected to succeed Dr David P. Barr, F.A.C.P., New York, N. Y., whose term expires June 30, 1945. Dr Schindler was elected for a term of three years, to 1948.

The suggestion was made by Dr Jonathan C. McKim, that the American Board of Internal Medicine consider the possibility of creating some additional Clinical Fellowships along the same line as proposed by the American College of Physicians.

President Irons called upon Dr Roger I Lee, as Chairman, to present the report of the Committee on Educational Policy

DR ROGER I LEE This Committee met on June 9 with General Morgan, Dr Irons and the Chairman present, and with Dr James J Waring of the Governors' Advisory Committee on Postgraduate Courses The Committee also had the advice of Doctors Paullin, Meakins and Barr, and of the Executive Secretary, Mr Loveland

The Advisory Committee on Postgraduate Courses, which is a Committee of the Board of Governors, has the responsibility of selecting courses to be given, subject to the approval of the Committee on Educational Policy and the Board of Regents The Committee voted to recommend that the Board of Regents approve the following program of courses for the autumn of 1945

Course No 1, *Allelgy*—Roosevelt Hospital, New York, N Y

Dr Robert A Cooke, Director

(one week—October 8-13, 1945)

Course No 2, *Internal Medicine*—University of Michigan Medical School, Ann Arbor

Dr Cyrus C Sturgis, Director

(two weeks—October 15-27, 1945)

Course No 3, *General Medicine*—University of Oregon Medical School, Portland

Dr Homer P Rush, Director

(one week—October 29-November 3, 1945)

Course No 4, *Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease*—Massachusetts General Hospital Boston Mass

Dr Paul D White, Director

(one week—November 5-10, 1945)

Course No 5, *Endocrinology*—University of Illinois College of Medicine, Chicago, Ill

Dr Willard O Thompson, Director

(one week—November 5-10, 1945)

Course No 6, *Gastro-enterology*—University of Chicago, Chicago, Ill

Dr Walter L Palmer, Director

(one week—November 12-17, 1945)

Course No 7, *Advanced Cardiology*—Philadelphia General Hospital, Philadelphia, Pa

Dr Thomas M McMillan, Director

(one week—November 26-December 1, 1945)

At the present time some men who are capable of directing excellent courses are unable to make positive commitments Consequently, there may be developed other courses, for which a mail vote may be necessary

After considerable discussion, the Committee voted to recommend through the Finance Committee that the Regents empower the President and Secretary-General to explore the possibility of securing an individual to act as the Educational Director under the Executive Secretary The Committee feels that a tremendous increase in the various activities of the College's educational program is to be anticipated The Executive Secretary carries the whole burden at the present time His one-time assistant has departed When the Annual Sessions are once more resumed, the executive work will be greatly increased

Commenting on the report, Dr Lee added "It was the feeling of this Committee and of the group that met with the Committee—the idea was initiated by the Executive Secretary—that the College is definitely pointing toward increasing activities along educational lines all the time, and with the cessation of hostilities there will

be a tremendous increase in these courses. It would be a step in the right direction. If a man could be found to add to the staff to act as director of the educational activities of the College, If the College were to embark upon this program it must face a real expense. This Educational Director would, of course, require a secretary and equipment, and he would require an expense account for travel, because one of the important things for him to do would be to get around the country, planning and carrying out the program. The Committee does not want the Board of Regents to feel that this can be done cheaply—it may not cost much for the balance of this year, but in time it would be a real expense, probably over \$10,000.00 annually. The Committee feels there is a definite trend in the College to make its educational activities a very prominent feature. We ought to get started in organizing this educational activity as early as possible. Mr. Loveland has done the work of this Educational Director and has done it extraordinarily well. He likes it and that is probably one of the reasons why it has been done so well. However, the Committee looks forward to the time when the Annual Sessions may be resumed, and those Annual Sessions and programs create a great deal of extra work for the Executive Secretary and his staff. If this proposal is approved and if a suitable Educational Director can be located, the Board could authorize his appointment through the Executive Committee, without having to wait until the next meeting of this Board in December."

**COLONEL MAURICE C. PINCOFFS** There is in the overseas medical profession a tremendous interest in what they may look forward to in regard to postgraduate activities after they get home. A great body of doctors are specializing in diseases of certain age periods, and there will be a demand for postgraduate courses, exceeding anything that we have experienced in the past. We should be prepared for that and should provide for a great expansion of the College activities in that direction. The College has had experience in this field, and it is in contact with all the educational facilities of the country. I am sure it has a great opportunity to meet what will really be an emergency in postgraduate education.

**DR. PLPPER** (as Chairman of the Committee on Finance) The principal of our Endowment Fund cannot be touched, only the income can be included in our annual surpluses. If we undertake all of the activities proposed at this meeting, we shall probably exceed our surplus. We estimated a surplus of \$10,000.00 for the current year, and this may reach as much as \$18,000.00, since we were not permitted to hold the annual combined meeting of the Governors and Regents. On the other hand, with the end of the War, our expenditures in some directions will be decreased and our income in other directions considerably increased.

**MR. E. R. LOVELAND** If such an officer is added to the College staff, I believe he could be of great service not only in connection with the courses, but also in connection with our program for post-war planning, and also in connection with the program of the Committee on Fellowships and Awards. It would certainly be worth while to follow up the accomplishments of our Research Fellows, and possibly to keep some close contact with the proposed Clinical Fellows.

On motion by Dr. Lee, seconded by Dr. Stroud, and unanimously passed the report of the Committee on Educational Policy was approved as a whole.

The Chairman called for the report of the Committee on Post-War Planning for Medical Service. Dr. Piersol, Chairman.

**DR. PIERSOL** Mr. Chairman, the meetings of the Committee on Post-War Planning have been held in Chicago during the past year, with one or more members representing the College present. The Central Committee has been enlarged by the addition of certain other agencies such as the American Hospital Association, the American Catholic Hospital Association, the Veterans Administration, the Army, Navy and Public Health Service. The meetings have been held largely at the headquarters of the American Medical Association, which is not called a central location, but the

organization has the facilities to conduct these meetings expeditiously and effectively. The various topics brought before the Committee have a national interest of wide application. It seems to the College Committee that the chief function of the Central Committee has been that of an advisory one, not actually doing many things, but directing and advising in their doing. Its activities and deliberations have made it possible for the leading national medical societies and agencies of this country to cooperate in a way which never before has been done, and to present a united front, as it were, on national problems of interest and important problems that are much too complex and involved for any single group to direct. It is the feeling of the members of this Committee that the Central Committee has really accomplished a very important and outstanding work. One of the most concrete things that has been done to date has been the establishment of a central bureau of information, which has available data by which it can give helpful suggestions to returning Medical Officers, both concerning educational possibilities and placement opportunities. The Central Committee does not intend to direct these men specifically, but has available the data desired. The efforts of the Central Committee have been directed toward utilizing wherever possible local agencies, rather than attempting to direct individual activity through the central group.

The College Committee met on June 9 and discussed many of the subjects which have already been taken up by the Committee on Fellowships and Awards and the Committee on Educational Policy, and curiously enough, and independent of those Committees, has arrived at much the same conclusions. We feel that the role of the College in the post-war medical period must be extended. We are convinced, from a study of questionnaires sent out to Medical Officers in the field, that the returning physicians want not generalities, but concrete suggestions as to the possibilities and plans for post-war medical training. In order to bring that about, the College should take a much more extensive and definite interest in this matter than heretofore. It should establish a fund adequate to carry on this work, its efforts to raise such a fund might well be supplemented by going to the Foundations and possibly certain commercial organizations, notably the manufacturers of drugs and medical equipment, who would welcome the opportunity to participate in this undertaking. We feel confident that should we embark on a definite program and lay it before such organizations, showing that we have ourselves appropriated a substantial sum of money, we could rapidly increase the funds available and enhance the results obtained. It is our belief that the activities of the College toward its members should be of a very personal character, that we should be in a position to offer them a personal service, in addition to anything that the Central Committee might be able to offer that we should be in a position to advise them on such matters as residencies, opportunities for research, and even possibilities for locations, if these members are returning and are uncertain as to what they should do. Furthermore, the College should continue in this educational field, to expand and to enlarge its short courses and other postgraduate activities, particularly in those specialties concerned with Internal Medicine. In order to implement these activities, there should be set in motion some machinery by which there could be a cooperative effort on the part of the Committee and of the Regents to cover the entire field of post-war medical planning. As you have already heard, the reports from the Committee on Fellowships and Awards and of the Committee on Educational Policy are in principle essentially the same as this report we are now presenting. To bring this program to fruition, steps should be taken to appoint someone, either part or full-time, to act as Educational Director, and to conduct the advisory activities that are contemplated. In order to make this possible, the Committee passed a resolution to recommend to the Regents that this plan be put into operation and to implement it, the Regents authorize an allocation of a sum of \$25,000.00. I move the adoption of the report.

The motion was seconded by General Morgan and opened for discussion

The discussion was directed toward clarifying and synchronizing the various recommendations of the Committee on Fellowships and Awards, the Committee on Educational Policy and Committee on Post-War Planning for Medical Service. There was general insistence that the program be immediately organized and not delayed for months to come. There was also insistence that an appropriation for administration be made separate from an appropriation for the program of fellowships and educational activities.

President Irons asked Dr. Piersol to further clarify his original recommendations for records.

DR. PIERSOL: "The Committee recommends the approval of the Board of Regents of the above educational plan, which includes the establishment of funds for training, the establishment of advisory personal service to help our Fellows and Associates in the matter of obtaining residencies, research or clinical fellowships, or advice as to their future locations, and an expansion of the short courses, particularly with reference to those courses in certain specialties. In order to carry out the activity, there should be appointed a full or part-time Educational Director under the Executive Secretary to carry on this work, as a coordinated program."

Dr. Piersol's motion and the one outstanding by Dr. Blake at the end of his report were amended and combined, providing that \$10,000.00 be appropriated for administration and \$25,000.00 be appropriated for Clinical Fellowships, and the motion was unanimously passed.

Numerous members of the Board emphasized the need for coordination of the efforts of all of these activities, and Dr. Piersol, in particular, as Chairman of the Committee on Post-War Planning for Medical Service, emphasized the recommendation that the entire educational program be carried out through the cooperative effort of all three Committees.

On motion by Dr. Piersol, seconded and regularly carried, it was

RESOLVED, that the Chairmen of the three Committees—Committee on Fellowships and Awards, Committee on Educational Policy and the Committee on Post-War Planning for Medical Service—shall draw up a concrete, specific educational program to implement the resolutions already adopted.

DR. MALKINS: Do you not think it is apparent that the time has arrived for the Board of Regents to appoint a Committee to take over all educational activities of these three Committees, irrespective of war or peace, and to remove from these other three Committees all activities dealing with educational training?

PRESIDENT IRONS: The Chair is not quite clear as to what other implications might come out of such a change. He is inclined to think Dr. Piersol's motion to have the three Chairmen meet and draw up their program is as far as we should go at this point.

DR. MALKINS: I concur.

#### Luncheon Recess

President Irons, resuming the meeting, called for the report of the House Committee.

Dr. William D. Stroud, Chairman of the House Committee, had nothing of significance to report. He said the maintenance of the building and grounds in fine condition is visible to all, installation of a new heating boiler proved not only necessary, but a good and economical investment, because the College had had adequate fuel under current restrictions for the past winter. The plumbing property owned by the College is under lease at a good rental until May 31, 1946.

The report was received with thanks.

President Irons then asked for the report of the Committee on Finance, Dr O H Perry Pepper, Chairman

DR PEPPER The Finance Committee met on June 9, 1945, at the College Headquarters, Drs Stone, Stroud, Tenney and Pepper and the Executive Secretary being present

- (1) The Committee presents to the Regents in printed form the details of the Employees' Retirement Plan, drawn up by the attorney of the College and the insurance company

The Committee recommends that the Regents rescind previous resolutions on this subject and adopt this printed document, thus legalizing all conditions of the Plan

- (2) The Committee reviewed the financial status of the College, and considers the situation satisfactory

There is an estimated surplus of \$10,330 00 for 1945, which will probably be increased by the failure to expend an item of \$7,500 00 in the budget for an annual meeting of the Officers, Regents and Governors

Factors influencing the situation include (a) a material increase in income from the ANNALS, (b) possible increase in costs of clerical and secretarial salaries in the Headquarters' staff, (c) possible cancellation of subscriptions to the ANNALS by the Armed Forces, (d) unforeseen expenditures

- (3) The Committee has approved suggestion of Drexel & Co for certain changes in investments and for the investment of uninvested funds When these are carried out, the College will have more than 50% of its funds in bonds 32% in common stocks, and 18% in preferred stocks The Committee considers this ratio satisfactory

According to Article VIII of the By-Laws the Regents must approve securities purchased for the Endowment Fund The Committee requests approval of the purchase for the Endowment Fund of approximately 16,000 United States Savings Bonds, Series G, 2½s

By resolution regularly passed, the report was approved and adopted

Dr Stroud, Treasurer, presented the following report

"A summary of the financial operations of the College for 1945 has already been submitted by the Committee on Finance The accounts of the College for 1944 were audited by a public accountant and his signed report has been inserted in the Minutes of this Board The net operating surplus for 1944 was \$23,628 25, all of which is in the Endowment Fund with the exception of \$609 40

"The book value or cost price and the present market price of securities held by the College are as follows

|                    | <i>Book Value</i> | <i>Market Value *</i> |
|--------------------|-------------------|-----------------------|
| General Fund       | \$134,389 10      | \$145,616 25          |
| Endowment Fund     | 167,519 78        | 191,893 75            |
|                    | <hr/>             | <hr/>                 |
|                    | \$301,908 88      | \$337,510 00          |
| Total Appreciation | 35,601 12         |                       |
|                    | <hr/>             | <hr/>                 |
|                    | \$337,510 00      | \$337,510 00          |
|                    | <hr/>             | <hr/>                 |

\* May 17, 1945

## OBITUARIES

### DR WILLIAM WORTHINGTON HERRICK

Dr William Worthington Herrick died suddenly on June 1, 1945, at the age of sixty-six. He was born at Sherman, Connecticut, February 19, 1879. His father, Edward Pierpont Herrick, was a clergyman. He received the degrees of A B in 1902 and M D in 1905 from Yale University. He served as intern at St Luke's Hospital, New York. He joined the faculty of Columbia College of Physicians and Surgeons in 1908, and advanced to Professor of Clinical Medicine, an appointment held for many years. His hospital positions were Attending Physician, Presbyterian Hospital and Sloane Hospital for Women, Consulting Physician, Woman's Beekman Street, Mary McClellan (Cambridge), Vassar Brothers (Poughkeepsie), Elizabeth A Horton Memorial (Middletown), Mount Vernon, Goshen, St Agnes (White Plains), White Plains, Stamford (Connecticut), Sharon (Connecticut), Greenwich (Connecticut), Nassau (Mineola) Hospitals, and New York Infirmary for Women and Children. He was a member of the Board of Trustees, Trudeau Sanatorium, New York State and County Medical Societies and the American Medical Association. He assumed office of President in the New York Academy of Medicine, January 1, 1945. was a Fellow of the American College of Physicians since 1919, and had been serving recently as a member of the Committee on Postwar Planning for Medical Service, and at one time was a Regent of the College. He was a Diplomat of the American Board of Internal Medicine and Editor-in-Chief of Nelson's Loose Leaf System.

Clinical medicine was Dr Herrick's passion. And he was most successful in its practice. Always keen in observation, a rare sense of values, a wealth of experience on which to draw and a highly developed power of integration placed him among the outstanding men in medicine both in New York City and the country. He loved to make rounds with students and interns. The students and interns loved to have him. Clinical pathological conferences for the students were his special delight and no one on the staff could surpass him in this exercise.

Dr Herrick had many interests outside the practice of medicine. He was fond of music, in fact had an organ installed in his home in Sharon, Connecticut. He played a good game of golf. He built furniture in his shop and was no mean wood carver. A large farm occupied much of his time and interest. In Sharon, his summer home, he was not just a "city folk" but took part in the community life and was sincerely interested in the welfare of the town's citizens. This interest was lifelong for in his early youth in the small village of Sherman, where his father was minister, he came to know the country people and had the greatest admiration for their simplicity, honesty and forthrightness, all characteristics prominent in himself.



Bill Herrick was a modest man. He was quiet, serious and reserved although the humorous side of life never escaped him. His opinions were expressed in few but carefully chosen words. He had the respect and admiration of his colleagues and associates and the affection of his friends. The College has lost one of its distinguished Fellows.

WALTER W. PALMER, M.D., F.A.C.P.,  
1st Vice President, A.C.P.

### COLONEL CHARLES GEORGE SINCLAIR

Colonel Charles George Sinclair, Medical Corps, U. S. A., Fellow of the American College of Physicians, died at Percy Jones General Hospital, Battle Creek, Michigan, May 3, 1945. Burial with full military honors was at Arlington National Cemetery, May 8, 1945.

Colonel Sinclair was born November 12, 1889 in Parkdale, Ontario, moving to Port Huron, Michigan, in 1892.

Education—B.S. 1912, M.D. 1914, University of Michigan, Assistant in Hygiene, University of Michigan, 1911–13, Internship, general, Providence Hospital, Washington, D. C. 1914–1915, Internship, communicable diseases, Willard Parker Hospital, New York City, 1922, Graduate, Army Medical School Basic Course, 1916, and Advanced Course in Preventive Medicine, 1921.

Military service—1st Lt., M.R.C., 1915, 1st Lt., M.C., 1916, advanced through the grades to Colonel, 1942, Temporary Colonel, 1941, Mexican Punitive Expedition, 1916, American Expeditionary Forces, France and Germany, June 1917 to October 1919. He was with the first troop convoy to France in 1917 and was battalion surgeon, 16th Infantry, which suffered the first battle casualties, November 3, 1917.

He served through World War I with the First Division and was commanding officer of the First Sanitary train in the Aisne-Marne, Montedier, Noyon, St. Mihiel, and Meuse-Argonne offensives. He was senior laboratory officer at Savenay, France, and of the base laboratory at Brest, France.

At various times on the instructional staff of the Army Medical School, including—Instructor in Pathology, 1925–27, Instructor in Bacteriology, 1927–30, and Instructor in Microbiology, 1925–30, tours of duty included Chief of Laboratory Service, 1925–27, Walter Reed General Hospital, Chief of Laboratory Service, 1933–35, Tripler General Hospital, Honolulu, Chief of Laboratory Service, 1935–40, Station Hospital, Fort Sam Houston, and Director of Preventive Medicine and Clinical Pathology, Army Medical School, 1940–42, Surgeon and Commanding Officer, Station Hospital, Camp Hood, Texas, 1942, Commanding Officer, Sixth Service Command Laboratory and Service Command epidemiologist, 1942 until his death.

In addition to several articles in medical journals he contributed to "Laboratory Methods of the U. S. Army," Lea & Febiger 1929, the section

on Bacteriology, War Department Technical Manual, "Methods for Laboratory Technicians," 1941, author of "Microbiology and Pathology," a textbook for student nurses, F A Davis Co (six editions)

Colonel Sinclair was the son of George and Margaret Jane Sinclair, deceased. He is survived by his widow, Margaret E Sinclair, two step-daughters, Miss John Campbell and Mrs Martin Fennell, and two sisters, Dr Elizabeth S Peck (Mrs John P ) instructor at Berea College, Kentucky, and Miss Olive V Sinclair, instructor at Port Huron Junior College, Michigan.

During his nearly thirty years of Army service he occupied many key positions with great credit to himself and to the military service. In failing health from malignant disease for over two years he continued to fulfill his duty in the Sixth Service Command in an exceptional manner until shortly before his death.

FROM THE OFFICE OF THE SURGEON GENERAL,  
U S ARMY

# ANNALS OF INTERNAL MEDICINE

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## ACUTE NON-SPECIFIC MYOCARDITIS \*

By SAMUEL CANDEL, Lt Comdr, (MC) USNR, and MARK C  
WHEELLOCK, Lt Comdr, (MC)USNR

A PECULIARLY anomalous situation exists in present day medicine. A mass of evidence has been collected by the pathologist to justify the recognition of an entity characterized by an acute inflammatory process involving the myocardium and most often secondary to some acute infectious disease, apart from the septicemias and the specific myocarditides occurring in such diseases as rheumatic fever, tuberculosis, and rarely syphilis. He has quite correctly labeled the condition as acute myocarditis. He has also on occasion demonstrated the same process apparently unassociated with any evident primary disease. He frequently decries the fact that the clinician does not make the diagnosis often enough. On the other hand, a mass of evidence has been collected by the internist to show that alterations of the electrocardiogram, from the mildest to the most profound, may and frequently do occur in the course of many acute and occasionally chronic infectious diseases, often in a most unanticipated fashion. If these same electrocardiographic alterations are observed in the course of acute rheumatic fever, in which the pathologic change involving the myocardium is well appreciated, they are accepted almost without exception as evidence of acute rheumatic myocarditis. Yet the vast majority of internists have been loathe to recognize these alterations as evidence of acute myocarditis or have merely overlooked the evidence when it was observed in the course of acute infectious disease, non-rheumatic in origin. The clinician has not been impressed with the significance of the electrocardiographic findings because almost all of these patients recover and practically no autopsy material is available from them to correlate lesions with the clinical observations. The pathologist will examine the myocardium in those who die of an acute infectious disease.

\* Received for publication December 21, 1944.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

From these he draws most of his conclusions. Usually the primary disease dominates the picture so much that a finding of myocarditis is interesting but very secondary. If the pathologist has an unusual interest in myocarditis, he is able to collect an appreciable number of cases, as Saphir<sup>1</sup> was able to do in his series of 240 cases in 5,626 autopsies. Sudden death, or death due to progressive myocardial insufficiency, has excited both the pathologist and internist, particularly when there was no history of antecedent disease and no primary disease was evident clinically, while at autopsy nothing but acute myocarditis was demonstrable. A number of such cases have been recorded in the literature under such titles as Fiedler's myocarditis, acute, subacute and chronic isolated myocarditis, acute, subacute, and chronic interstitial myocarditis, idiopathic myocarditis, primary myocarditis<sup>2, 3, 4, 5, 6, 7, 8, 9, 10</sup>

Hansman and Schenken<sup>5</sup> are of the opinion that acute isolated myocarditis differs etiologically from the acute toxic myocarditis which is caused by infectious disease only in that the origin of the infectious agent is obscure. We concur in this opinion. The cases of acute isolated myocarditis recorded in the literature, although relatively few, are of great importance. They pose the question as to whether or not they represent a particular group of cases of heart disease which always terminates fatally, or whether they represent only some of the fatalities of a larger group of acute myocarditis, non-specific in nature, in which the majority recover even though they have never been recognized clinically, whereas the minority, likewise not recognized clinically, do not recover and at autopsy show acute myocarditis.

Scherf and Boyd,<sup>11</sup> who have written an excellent account of acute myocarditis, say "the frequency and significance of myocarditis has been evaluated very differently in the course of recent years. There were and at present still are physicians who designate almost every myocardial disease as myocarditis or fibroid myocarditis, providing a valvular lesion is excluded, despite the presence of a definite coronary sclerosis or cardiac failure from an associated hypertension. Against this generalization, a very natural adverse reaction has developed and at many very estimable institutions myocarditis is designated as a rare affection which can be diagnosed clinically only in exceptional cases. Neither attitude is correct. Sufficient evidence has been collected to prove that myocarditis has not been correctly appraised in regard to its importance or frequency. Myocarditis is a common disease and quite often remains unrecognized."

Maher and Wosika<sup>12</sup> have noted "that the frequent association of myocardial injury with acute infections is not as common knowledge as it should be. Injury to the myocardium and the intimately associated conduction system is undoubtedly more frequent than we know."

We wish to record the cases of 11 patients whom we have observed clinically and in whom the clinical diagnosis of acute myocarditis was made. The evidence for the diagnosis is presented. We shall also record a case of

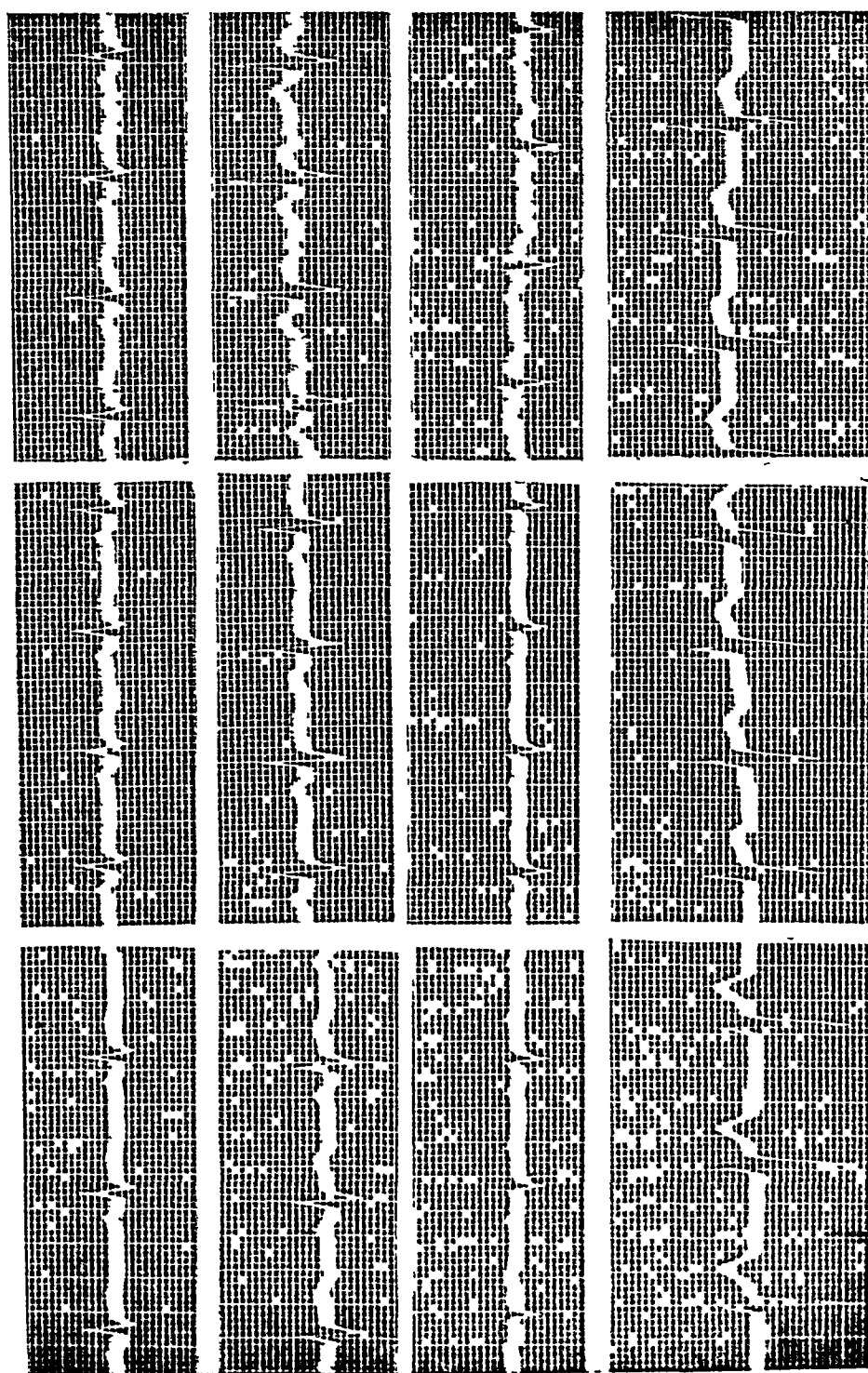


Fig 1 Case 1 Diagnosis Peritonissilar abscess, acute non-specific myocarditis  
 Inversion of T-waves in  $L_2$  and  $L_3$  on fifth day  
 Flattening of  $T_1$  and  $T_2$  on second day

tonsillitis, which was observed at another institution and autopsied by one of us

### CASE REPORTS

#### *Case 1* Diagnosis Peritonsillar abscess, acute non-specific myocarditis

W P, an officer aged 28 years, complained of difficulty in swallowing for one day. His temperature on admission was 100° F. Examination showed a left peritonsillar abscess which was incised 48 hours after admission. The erythrocyte sedimentation rate on the second day was 25 mm in one hour (Cutler method). He improved rapidly and was discharged on the sixth day.

Because of the marked toxemia and our academic interest in this instance an electrocardiogram was taken on admission.  $T_1$  was low. There was a left axis deviation (figure 1). On the second day  $T_1$  and  $T_2$  were practically isoelectric and  $T_3$  was lower. On the fifth day  $T_2$  and  $T_3$  became inverted.

*Comment.* A diagnosis of acute myocarditis was made on these electrocardiographic findings. The officer was returned to duty on the sixth day. This was an obvious error on our part.

#### *Case 2.* Diagnosis Pneumonia, lobar; acute non-specific myocarditis

J H, S2c, aged 34 years, was admitted one day after a severe chill, followed by fever, cough, and bloody expectoration. His temperature was 103° F, pulse 88 with extrasystoles, respirations 18, blood pressure 130 mm Hg systolic and 70 mm diastolic. There was dullness over the left lower lung posteriorly and numerous crepitant râles were heard. The heart was not enlarged to percussion. There were no murmurs. Gallop rhythm was present. Roentgenogram showed consolidation of the left lower lobe. During the examination the patient felt faint and broke out into a profuse perspiration. An electrocardiogram was taken. It showed bundle branch block (common type) with occasional extrasystoles. He became afebrile on the sixth day but complained of weakness. An electrocardiogram done on that day still showed bundle branch block with variations in QRS and T-waves and a P-R interval of 0.30 second. Subsequent studies showed variations of the dominant bundle branch block and the last electrocardiogram done on the ninety-sixth day still showed the bundle branch block and a P-R interval of 0.30 second (figure 2). The erythrocyte sedimentation rate on admission was 23 mm (Cutler) in one hour. It remained rapid for 90 days when it fell to 15 mm per hour.

*Comment.* It is our opinion that the bundle branch block was probably a consequence of the pneumonia and did not precede it. This is borne out by the fact that the pattern of the electrocardiogram continued to change during the period of observation (see F-wave changes in  $L_2$  and  $L_3$ ).

*Case 3.* Diagnosis Pneumonia, primary atypical, etiology unknown, acute non-specific myocarditis.

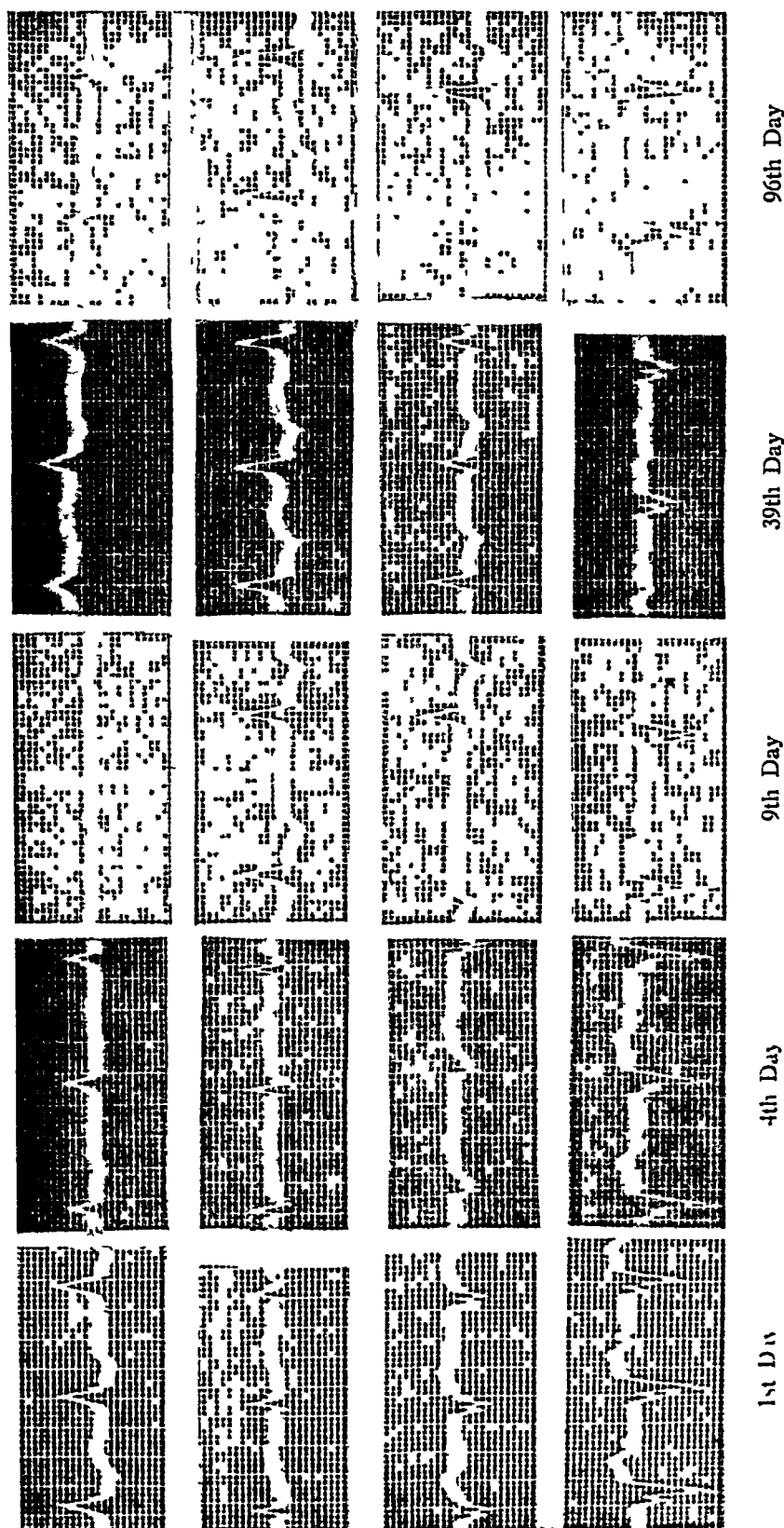
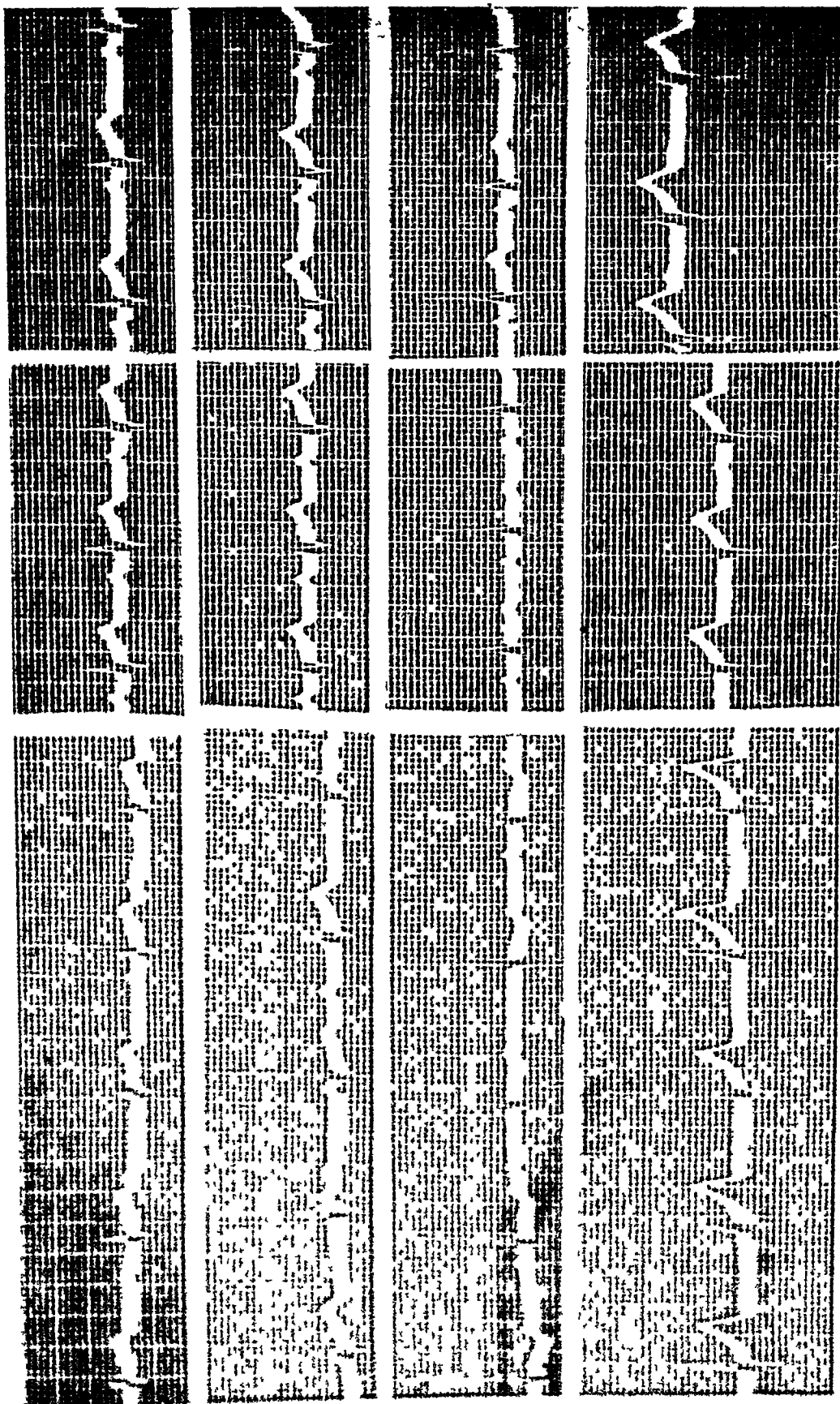


FIG. 2. Case 2. Diagnosis: Lobar pneumonia, acute non-specific myocarditis. Electrocardiograms on first and fourth days show bundle branch block, common type. In the three subsequent electrocardiograms, note the variations in direction of QRS, and T, while QRS, in the last two tracings runs upright. The last three tracings are therefore still consistent with diagnosis of bundle branch block, common type.



57th Day

64th Day

72nd Day

Diagnosis: Pneumonia, primary atypical, etiology unknown, acute non-specific myocarditis. Discharged to duty 48 days after admission for pneumonia. Readmitted 14 days later (fifty-seventh day) because of breathlessness. First tracing compared to admission. Second tracing normal rhythm with P-R interval 0.20 second. Third tracing normal rhythm, P-R interval 0.14 second.



later the electrocardiogram showed a normal rhythm with a P-R interval of 0.20 second. Fifteen days after admission the rhythm was normal and the P-R interval 0.14 second. The erythrocyte sedimentation rate was 23 mm in one hour on the eighth day and 7 mm on the thirty-eighth day. He was returned to duty 45 days after this second admission.

**Comment** This is an example of acute myocarditis following pneumonia. The symptom of breathlessness, coupled with the suspicion that it might be due to myocarditis following an acute infection, led to the diagnosis.

**Case 4** Diagnosis Scarlet fever, acute non-specific myocarditis

J. A. S., S2c, aged 18 years, entered the hospital on January 21, 1944 with a sore throat and a typical scarlet fever rash. Temperature was 100.4° F on admission and rose to 104° on the fourth day. His tonsils were inflamed. The *Streptococcus anhemolyticus*, gamma was cultured from the throat. He developed a cervical lymphadenitis on the fourteenth day. This subsided and he became afebrile on the nineteenth day of disease. On the latter date he began to complain of pains in the knees and ankles. There was no evidence of swelling, no tenderness, and no pain on motion. The erythrocyte sedimentation rate was 28 mm, per hour. The heart was not enlarged. There were no murmurs. An electrocardiogram done on the twenty-third day showed an inverted T<sub>1</sub> and T<sub>4</sub> and a low T<sub>2</sub> (figure 4). Two days later T<sub>2</sub> became almost isoelectric. On the thirty-ninth day T<sub>1</sub> and T<sub>2</sub> were again upright and T<sub>4</sub> was biphasic. On the fifty-seventh day a normal tracing was obtained. Roentgenogram of the chest showed a normal cardiac configuration. The erythrocyte sedimentation rate became normal on the thirty-first day. He was permitted out of bed on the fortieth day and was discharged on the sixty-first.

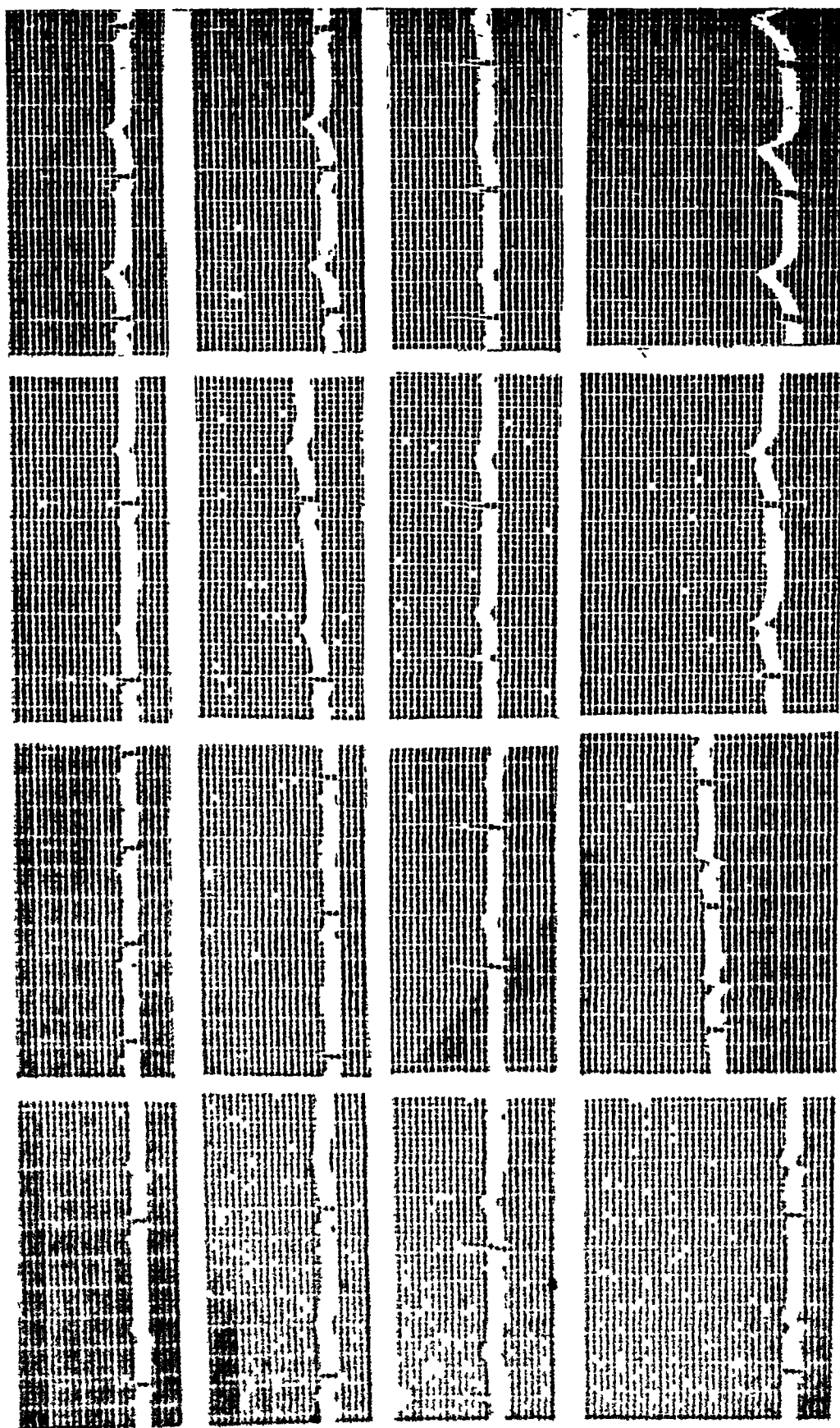
**Comment** This is an example of acute myocarditis following scarlet fever. Our attention was focused on the heart because of the arthralgias and the possibility of a complicating rheumatic infection.

**Case 5** Diagnosis Acute recurrent gonococcal arthritis, acute non-specific myocarditis

F. G. O., BM1c, aged 38 years, gave a history of gonorrheal urethritis in October 1943. One week after the onset of the urethral discharge, he developed swelling and pain of the left ankle, knee and wrist. He was confined to bed for four weeks and then sent to duty.

The man was later transferred to this activity, where, on March 31, 1944, he was admitted to the sick bay with a story of pain and swelling of the right wrist and ankle for one week. Temperature was 101° F. All findings were negative except for swelling and tenderness of the right wrist and ankle. The erythrocyte sedimentation rate was 25 mm in one hour. Roentgenogram of the chest showed heart normal in size and shape. He had a low grade fever, not over 100° F, for six weeks. The inflamed joints did not respond to large doses of salicylates or to a course of sulfadiazine. After five weeks, pain, tenderness and swelling of the joints subsided. The wrist and ankle, however, showed much periarticular thickening. An electrocardiogram done on the eleventh day after admission (eighteenth day of disease) showed a low T<sub>1</sub> and an inverted T<sub>4</sub> (figure 5). On the twenty-seventh day of disease T<sub>1</sub> was practically isoelectric. On the thirty-seventh day T<sub>1</sub> was higher and T<sub>4</sub> became positive. The electrocardiogram on the sixty-fourth day showed T<sub>1</sub> to be normal. The sedimentation rate was 26 mm on the sixtieth day; 30 mm on the seventy-fourth day. The sedimentation rate was still rapid on the eighty-fourth day and the man was transferred to another activity.

**Comment** This man had a gonococcal arthritis, as evidenced by history of previous attack, failure of the joints to react to salicylates and the residual thickening of the involved articulations. The electrocardiogram gave evidence of myocardial damage.



25th Day      39th Day      57th Day  
 Normal tracing on the fifty-seventh day      T-wave inversion in Leads I and IV, T, T<sub>2</sub> changes in

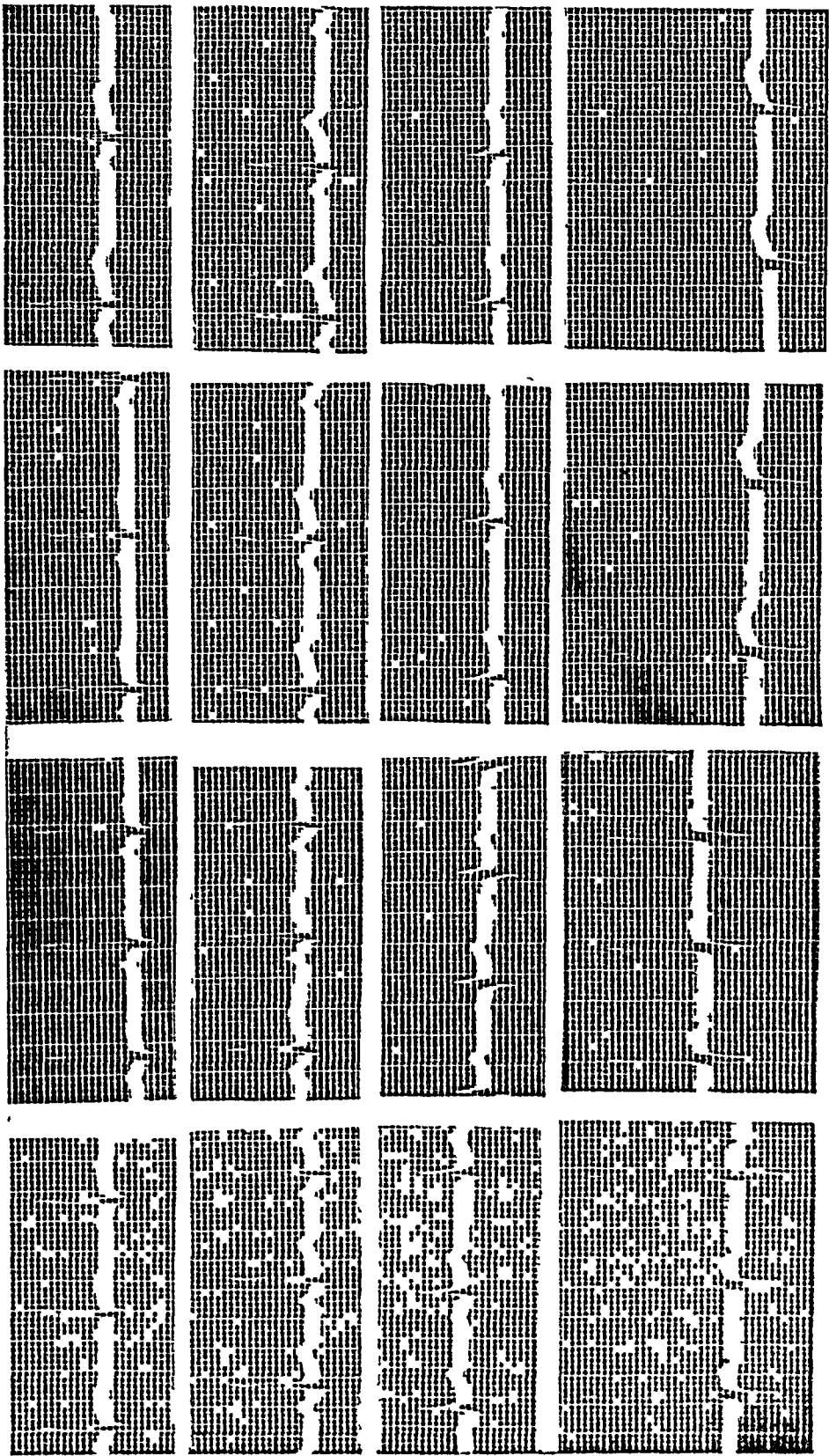


Fig. 5 Case 5. Diagnosis  
18th Day  
Acute recurrent gonococcal arthritis, acute non-specific myocarditis  
Normal tracing on sixty-fourth day  
37th Day  
64th Day  
T-wave changes in  $L_1$  and  $L_4$

*Case 6* Diagnosis Acute gonococcal arthritis, acute non-specific myocarditis

R L B, S2c, aged 19 years, was treated for a specific urethritis on March 11, 1943. After a course of sulfathiazole the urethral discharge ceased. On March 20 he had a recurrence of his urethral discharge. This was associated with swelling of the right great toe and right knee. On admission, March 21, both knees were swollen. Temperature was 101° F. The temperature was elevated daily up to at least 100° F for two months. Both ankles became swollen. The right sternoclavicular joint likewise was involved. The arthritis was non-migratory. When the process subsided, the joints were left with periarticular thickening. On April 3, 100 cc of a cloudy, straw-colored fluid were aspirated from the right knee. Gram negative diplococci were demonstrated in the fluid. The arthritic process was refractory to a full course of sulfathiazole and to massive doses of salicylates. The erythrocyte sedimentation rate, rapid on admission, was still 30 mm in one hour at the end of two months. There was no evidence clinically of cardiac abnormality. Roentgenogram of the heart showed it to be normal in size and shape. An electrocardiogram done on the twelfth day after the onset of arthritis was within normal limits (figure 6). On the twenty-sixth day  $T_1$  was low,  $T_2$  diphasic,  $T_4$  became inverted. On the sixty-sixth day  $T_1$  had become more positive. On the ninetyeth day  $T_4$  was again upright and the electrocardiogram more nearly approached the normal.

Comment A case of gonococcal arthritis showed electrocardiographic evidence of myocarditis over a period of three months.

*Case 7* Diagnosis Acute gonococcal arthritis, acute non-specific myocarditis

S S, S2c, aged 37 years, was treated on February 12, 1944 for gonococcal urethritis. One week later he developed swelling of the right knee. He was admitted to the sick bay. Both knees, both ankles and the right large toe became involved. The arthritis was non-migratory and was not affected by salicylates or sulfadiazine. On March 21, a course of penicillin for one day resulted in prompt subsidence of urethral discharge. The erythrocyte sedimentation rate was 27 mm on admission and became normal on the eighty-seventh day. He was returned to duty three and one-half months after admission. On February 19, the day of onset of arthritis, an electrocardiogram was normal (figure 7). On February 23  $T_1$  was biphasic,  $T_2$ ,  $T_3$  and  $T_4$  were inverted.  $I_1$  became upright on the twelfth day after onset of arthritis.  $I_1$  became positive but remained low on the fourteenth day. On the fifty-first day  $T_1$  and  $I_1$  were still low.

Comment A case of acute gonococcal arthritis was complicated by acute myocarditis as shown by the changes in the electrocardiogram.

*Case 8* Diagnosis Stricture urethral, urinary retention, cystitis, acute, acute non-specific myocarditis

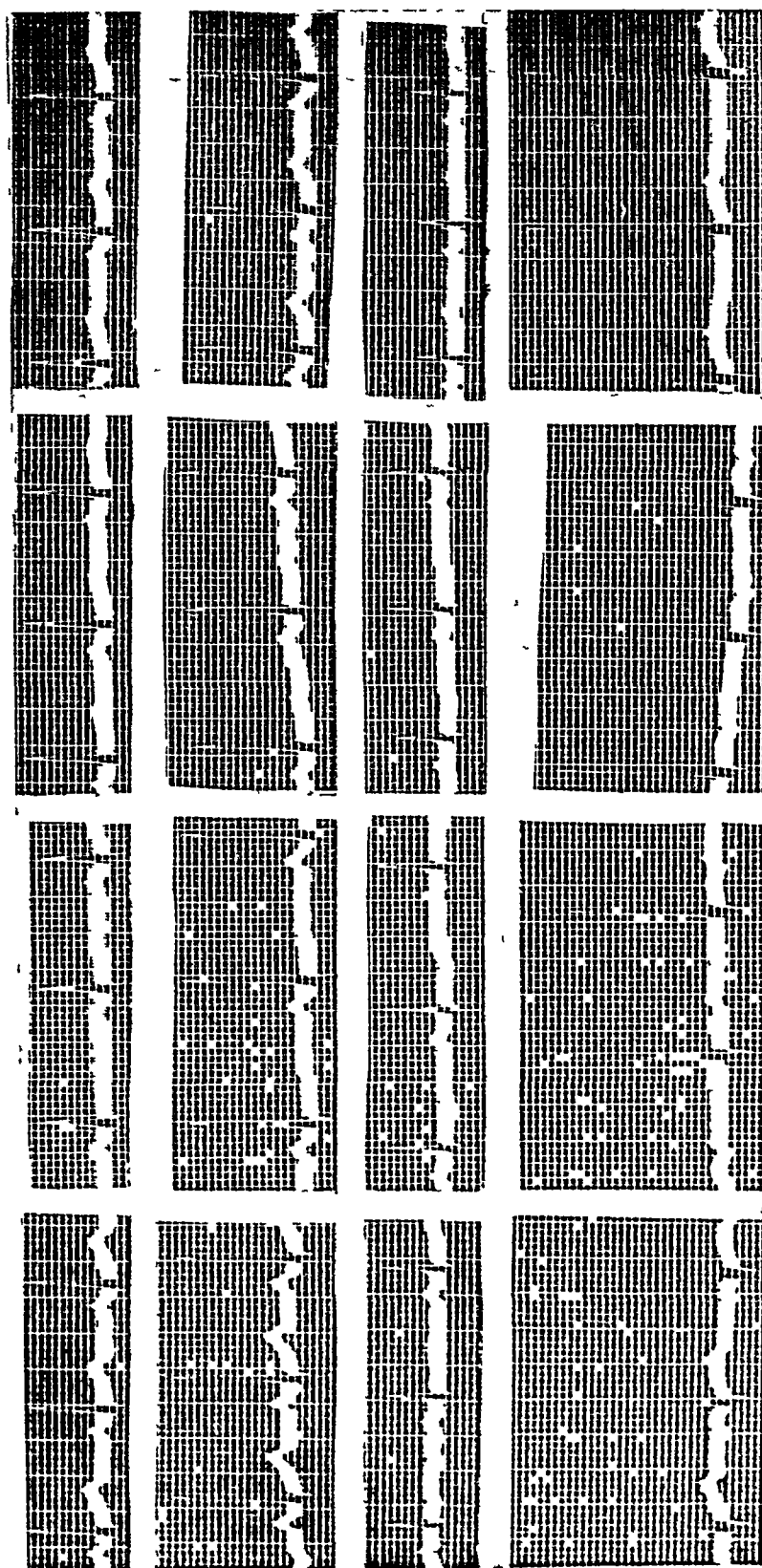
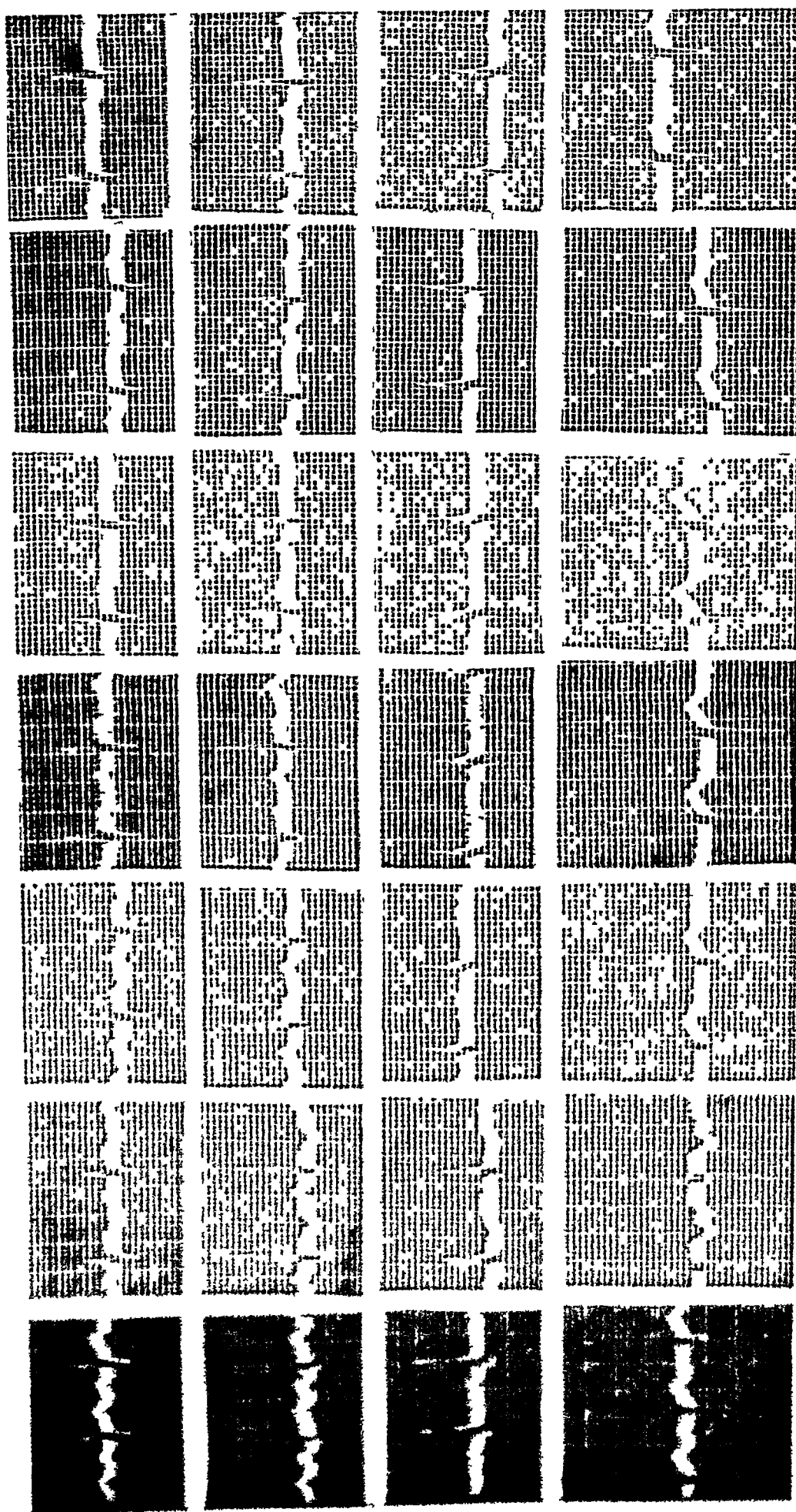


Fig. 6. Case 6. Diagnosis: Acute gonococcal arthritis, acute non-specific myocarditis. T-wave changes in L<sub>1</sub>, L<sub>2</sub>, L<sub>3</sub>, L<sub>4</sub>, normal tracing on ninetieth day.





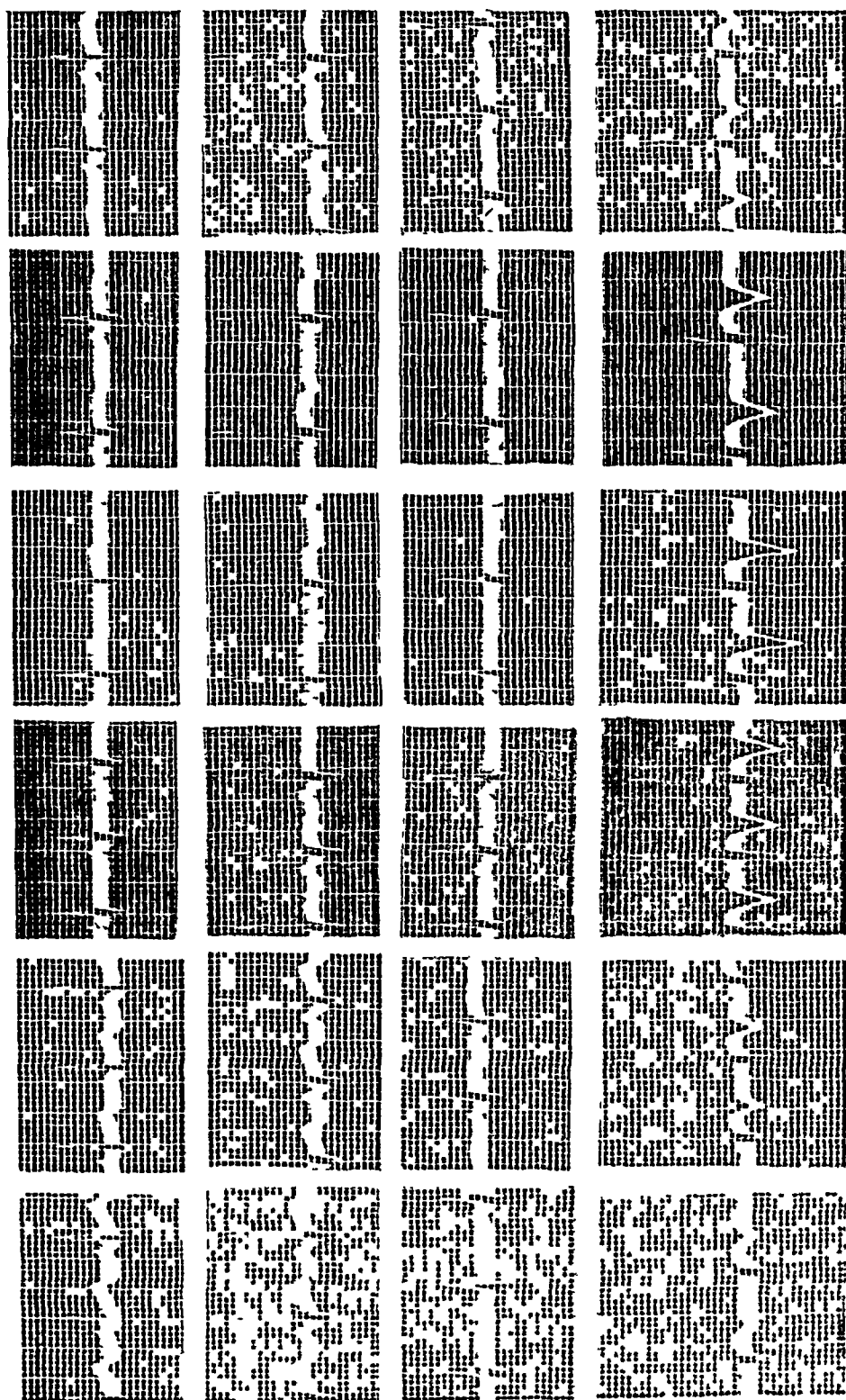


FIG. 8. Case 8. Diagnosis: Structure, urethral, cystitis, acute, acute non-specific myocarditis. First electrocardiogram taken on first post-operative day following the last procedure, i.e. 37 days after original admission. F-wave changes in I, II, L<sub>1</sub>, and L<sub>1</sub>.

as to size and shape. An electrocardiogram done on February 10 showed a sinus tachycardia with a biphasic  $T_4$  (figure 8). Another tracing four days later showed a marked inversion of  $T_4$ . On the thirteenth day after the first tracing,  $T_1$  was isoelectric,  $T_2$  was low, and  $T_4$  was sharply inverted. On the twenty-third day  $T_1$  was biphasic,  $T_2$  inverted,  $T_4$  a little less inverted. On the twenty-ninth day  $T_1$  was upright,  $T_2$  was upright,  $T_4$  was becoming less negative.

**Comment.** This was a case of acute cystitis, with a tachycardia and electrocardiographic evidence indicative of an acute myocarditis.

**Case 9.** Diagnosis: Infectious mononucleosis, acute non-specific myocarditis.

R. H. C., Lt (jg), aged 24 years, had a sore throat on May 2, 1944. His temperature on admission was  $100.2^{\circ}\text{F}$ . The erythrocyte sedimentation rate was 5 mm in one hour. For the first two weeks the temperature was low grade and did not exceed  $100^{\circ}\text{F}$ . Blood counts were reported as normal. On May 16 a blood count showed 4,900 cells with 62 polymorphonuclear cells, 35 lymphocytes and 3 monocytes. On May 18 the spleen was palpable and the right submaxillary nodes were swollen and tender. On May 22 the erythrocyte sedimentation rate was 18 mm in one hour. He developed a generalized lymphadenopathy. On May 24 a blood count showed 11,400 cells with 31 per cent polymorphonuclear leukocytes and 69 per cent lymphocytes. Many of the lymphocytes were atypical and characteristic of infectious mononucleosis. A heterophile agglutination test was positive in a dilution of 1-2560. From May 14 to May 28 he ran a stormy febrile course with elevations reaching  $103^{\circ}\text{F}$  daily. During the next two weeks he showed a low grade temperature, which became normal. Serial electrocardiograms showed a biphasic  $T_4$  on the seventeenth day (figure 9). On the twenty-second day  $T_4$  was upright,  $T_3$  isoelectric,  $T_2$  a little low.  $T_4$  changes were again noted on the twenty-fourth and thirty-first days.

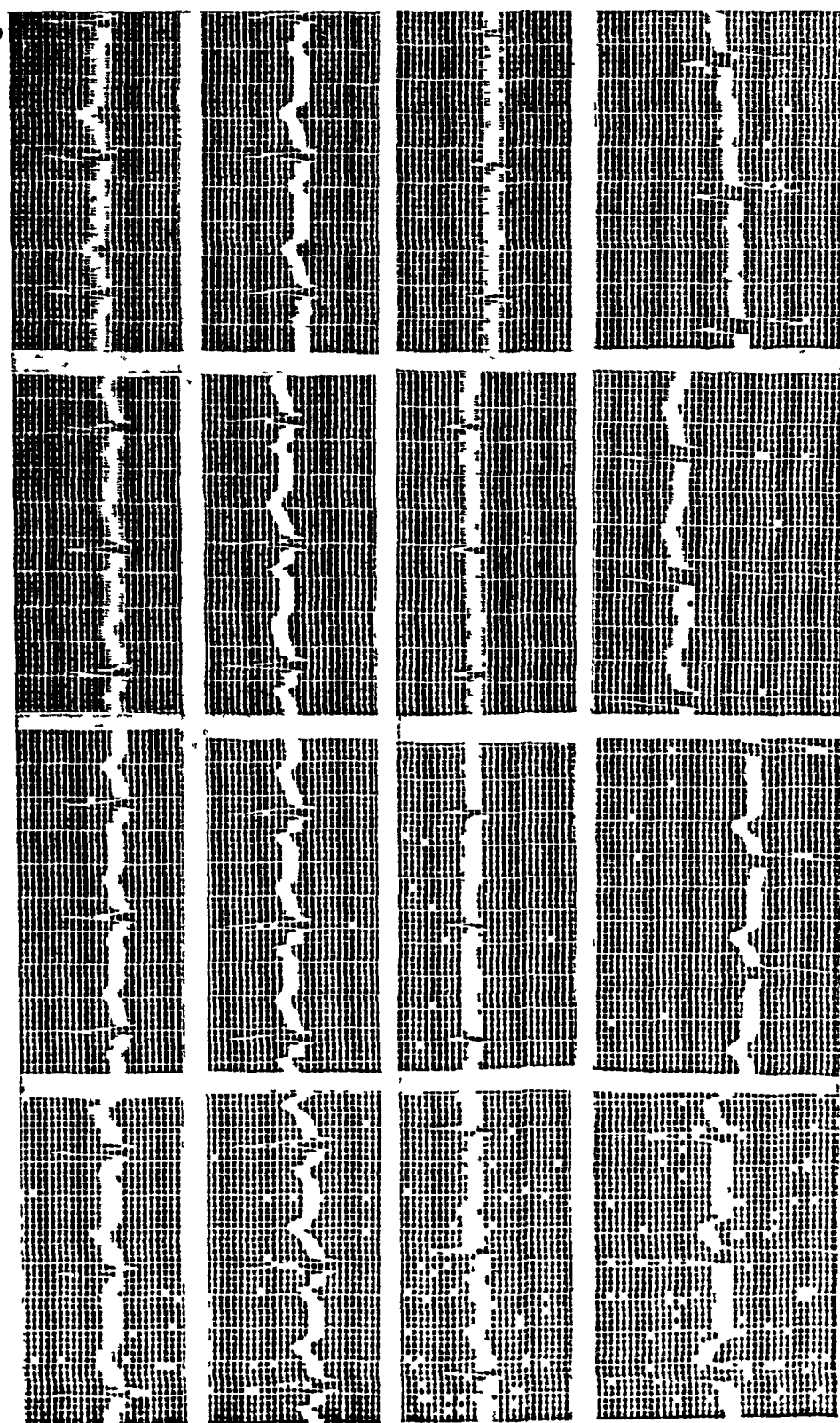
**Comment.** The electrocardiographic alterations were indicative of myocarditis in the course of a case of infectious mononucleosis.

**Case 10.** Diagnosis: Typhus fever, acute non-specific myocarditis.

S. P., Sic, aged 23 years, was admitted on April 21, 1944 with a sore throat, chills, fever and headache. On April 28 he developed a fine macular eruption. On April 28 the Weil-Felix reaction was positive in dilution of 1-80 and on May 9 the Weil-Felix reaction was positive in dilution of 1-320. He became afebrile on the eleventh day. The erythrocyte sedimentation rate was 16 mm on the fifth day and 19 mm on the twentieth day. It was normal on the forty-ninth day. An electrocardiogram on the ninth day showed a P-R interval of 0.28 second. On the fifteenth day it was 0.30 second, on the twenty-sixth day, 0.24 second, on the thirty-seventh day, 0.20 second. It was still 0.20 second on the seventy-ninth day (figure 10).

**Comment.** The varying abnormal P-R intervals were indicative of an acute myocarditis.





17th Day                      22nd Day                      24th Day                      31st Day  
 Fig 9 Case 9 Diagnosis Infectious mononucleosis, acute non-specific myocarditis T-wave changes in L<sub>1</sub>

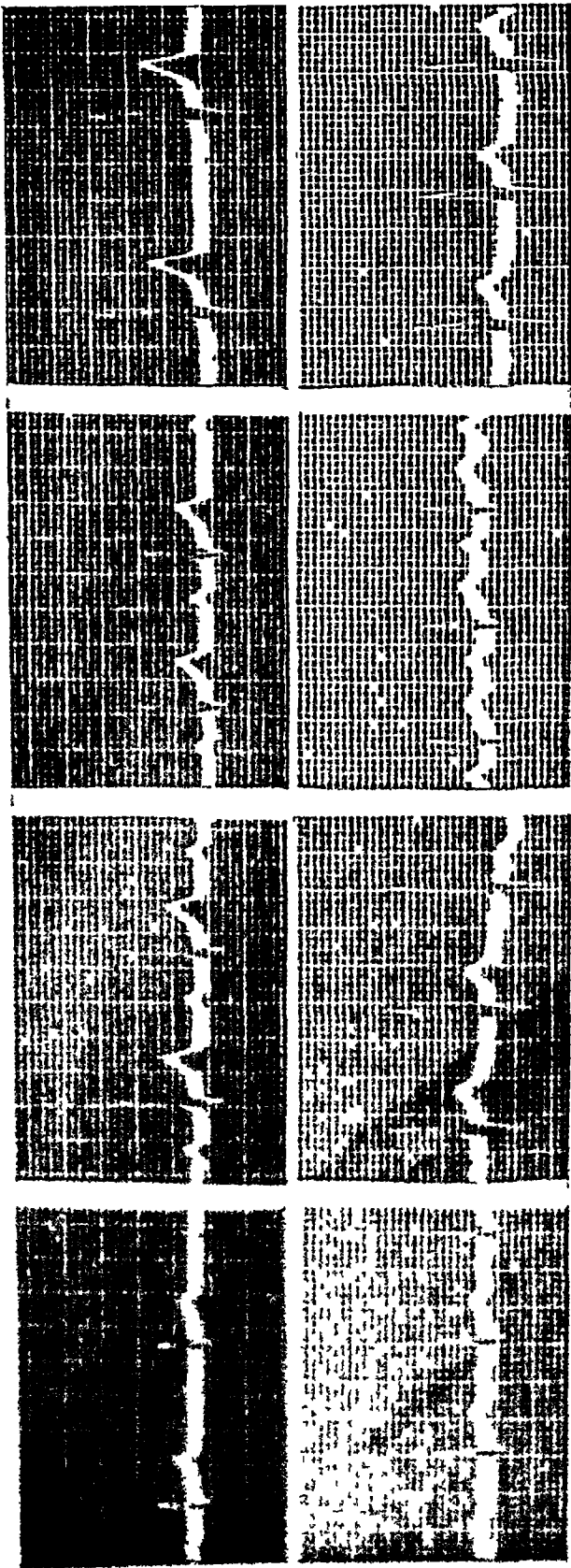


Fig. 10. Case 10. Diagnosis Typhus fever, acute non-specific myocarditis. P-R interval prolonged. Electrocardiograms showed P-R intervals of 0.28 second on the ninth day, 0.30 second on the fifteenth day, 0.24 second on twenty-fifth day, 0.21 second on thirty-sixth day, 0.20 second on seventy-ninth day. Only tracings on fifteenth and seventy-ninth days are reproduced.

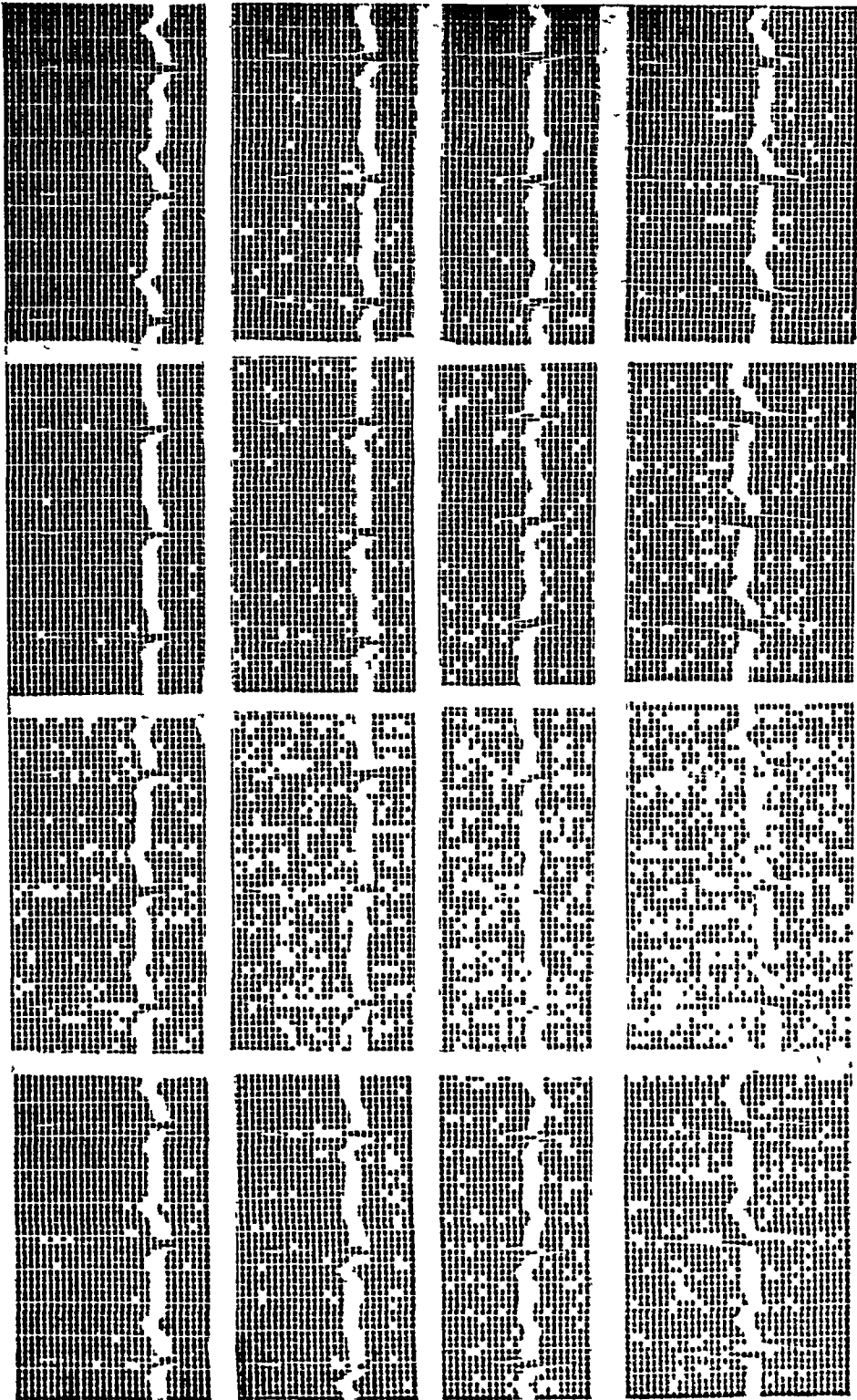


Fig 11 Case 11 Diagnosis Typhus fever; acute non-specific myocarditis T<sub>2</sub> low on the fourth day T<sub>1</sub> low and biphasic and T<sub>2</sub> inverted on the fifteenth day T<sub>1</sub> upright and T<sub>2</sub> upright although still low on the nineteenth day

An electrocardiogram done on the fourth day of disease (second day after admission) showed a left axis deviation and a low  $T_2$ . The electrocardiogram was repeated every three days. There was no variation until the twelfth day when  $T_2$  was a little flatter. On the fifteenth day  $T_1$  was biphasic and  $T_2$  inverted. On the nineteenth day  $T_1$  had returned to normal and  $T_2$  became upright but was still low.

Comment. A case of typhus fever showed electrocardiographic evidence of acute myocarditis as shown by T-wave changes in  $L_1$  and  $L_2$  of the electrocardiogram.

The 11 cases just presented had the following characteristics in common:

- (a) Each was associated with an acute infectious disease with the additions that case 3 was seen two weeks after discharge from treatment for pneumonia and case 5 had an acute recurrence of a gonococcal arthritis.
- (b) Each showed significant electrocardiographic alterations.
- (c) Each had a rapid erythrocyte sedimentation rate even when the primary disease had apparently abated (with the exception of case 8, where no erythrocyte sedimentation rate was done).

Attention was drawn to the possibility of acute myocarditis in case 2 because of extrasystoles and a gallop rhythm, in case 8 because of a persistent tachycardia without fever, in case 3 because of the symptom of breathlessness. Attention was focused on the electrocardiogram in cases 4, 5, 6 and 7 because most observers are conditioned to look for evidence of myocarditis in any disease in which joint symptoms are prominent. Cases 1, 9, 10 and 11 were studied because of marked toxemia and our curiosity to see if there were any evidences of myocardial involvement by the underlying disease.

We did not attempt to carry on any investigation of all the patients with acute infections or severe toxemia who came under our observation. We can make no statement, therefore, as to the frequency of occurrence of acute myocarditis. These 11 cases merely represent 11 observations collected during the past months.

Case 1 in our series was one of acute myocarditis, secondary to a peritonsillar abscess. Scherf<sup>1</sup> published five cases of acute myocarditis following tonsillar infection. One of these followed a peritonsillar abscess. In Scherf's experience, 10 to 15 per cent of patients with acute tonsillitis develop symptoms, signs or electrocardiographic changes which suggest myocardial involvement. He found that the occurrence of myocarditis ap-

concrete evidence and practically no observation at autopsies are available to answer the question whether myocardial changes occur as a result of tonsillar infections. There are students who believe that fleeting electrocardiographic changes signify anatomic lesions, whatever they may be. There are others, more cautious, who do not accept the statements as to myocarditis in these without more anatomic proof than is available today."

We wish to record a case of acute suppurative tonsillitis followed by sudden death due to acute non-specific myocarditis. This patient was seen by neither of us clinically, but was autopsied by one of us at another institution.

F. D., male, aged 24, was admitted to the hospital on December 30, 1943. He appeared moderately ill and stated that his illness began two days previously with headache, malaise, congested nose, sore throat and fever. Physical examination was negative except for a moderately injected pharynx, congested nasal mucosa, and a temperature of 101° F. The following day, December 31, he appeared comfortable and had a temperature of 102° F. Physical examination showed an increased redness of the pharynx. His tonsils appeared moderately swollen and red. He was given sulfathiazole, one gram every four hours. On January 1, 1944, his temperature was 99° F. He felt better. His tonsils were less swollen. He sat up in bed, conversed with patients around him. He was seen to go to the head. On January 2, 1944 he awoke at 0010 and spoke to an attendant. He made no complaint and appeared well. At 0600 he was found dead in bed.

An autopsy, including examination of the brain, was done. The most significant findings described in the protocol are summarized.

Cultures from the throat and nasopharynx showed the *Streptococcus hemolyticus beta*.

In the pharynx there was marked hyperplasia of the faucial and lingual tonsils with prominent crypts which were filled with thick purulent exudate. A similar exudate was present in the nasopharynx.

The heart weighed 387 grams. The right ventricle was 2 mm in thickness and the left ventricle was 15 mm in thickness. The valve measurements in circumference were as follows: tricuspid, 13 cm; pulmonary, 5 cm; aortic, 5.2 cm; mitral, 9 cm. The heart on inspection was increased in size owing to dilatation of the right ventricle. This was substantiated by the measurements as given above. The epicardium was smooth, glistening and transparent. There was some fat deposited over the right ventricle. In addition, there were small ecchymoses beneath the epicardium along the atrioventricular sulci. The heart muscle was soft, reddish-brown, and contained yellow and gray streaks running through it. The valve leaflets were soft and pliable and there were no adhesions. The endocardium was smooth throughout except in the left atrium where there were some small linear streaks of fibrous thickening. Sections through the interventricular septum showed the changes in the myocardium already described. The coronary arteries were patent throughout. There was a yellow deposit in the intima of right and left coronary arteries. The aorta was elastic and contained yellow deposits similar to those present in the coronary vessels.

*Microscopic Examination.* Heart wall, left ventricle. The epicardium showed a thin layer of fibrin on the surface and an infiltration of polynuclear cells. There was very little fat present. In the myocardium there was pronounced fragmentation of the bundles with the loss of the usual cross striations. In addition there was a widespread diffuse infiltration of the interstitial tissue by polynuclear cells. There was a very slight tendency for the inflammatory reaction to be perivascular. No Aschoff nodules or cells were present. The endocardium was locally thickened over

the papillary muscles and contained scattered polynuclear cells in its underlying tissue. A second section of heart wall from the left ventricle showed those changes already described, but of a more widespread character (figures 12 and 13)

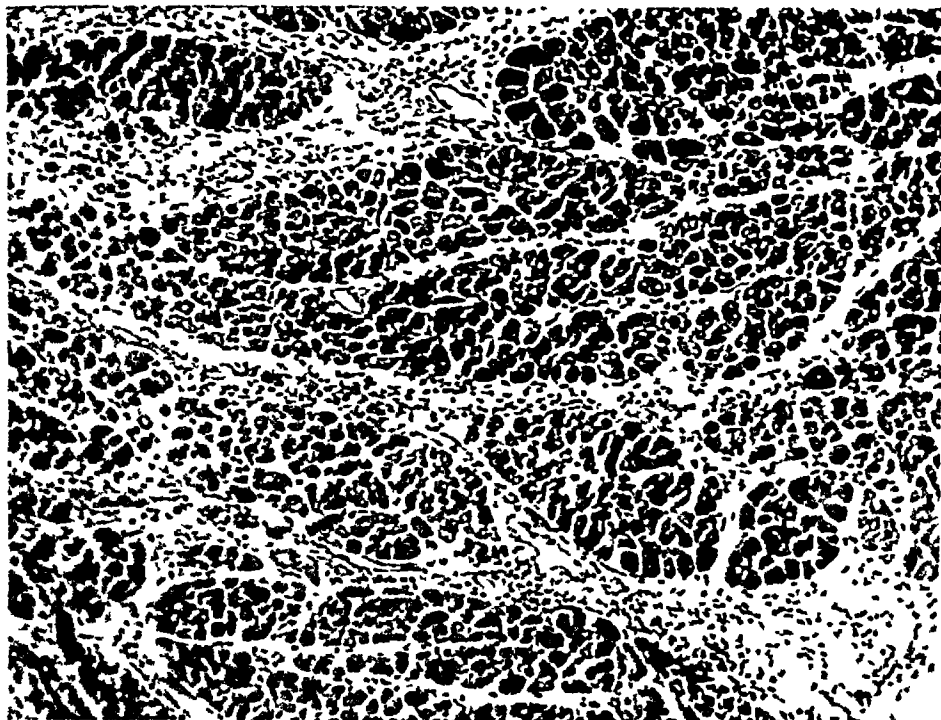
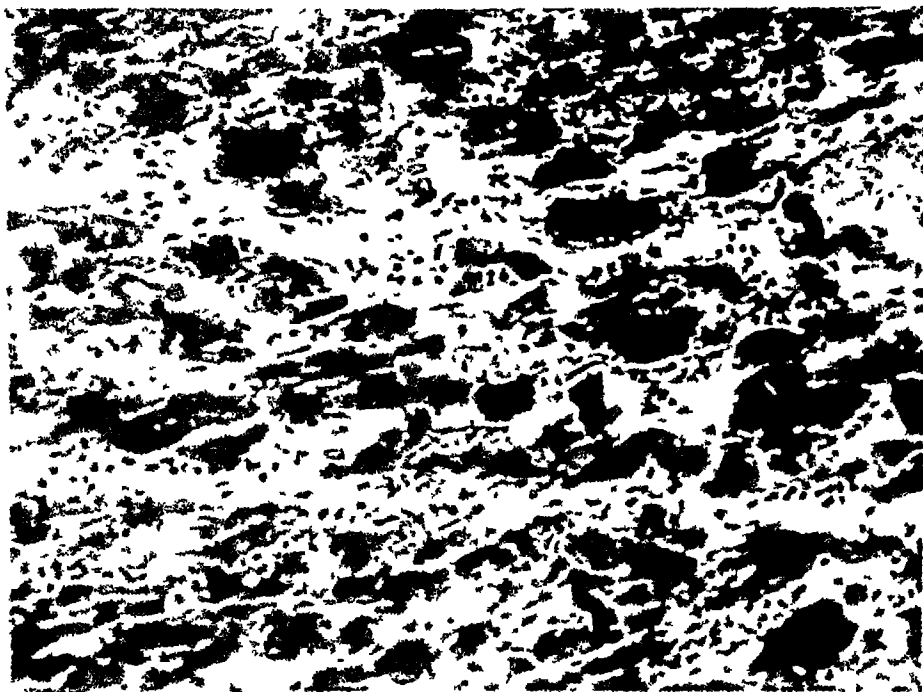


FIG. 12. Acute non-specific myocarditis following acute suppurative tonsillitis. Low Power. Diffuse infiltration of myocardium by polymorphonuclear leukocytes.



Atrium There was a slight thickening of the endothelium

Pulmonary artery Normal

Heart wall Right ventricle showed a minimal amount of fat infiltration The acute inflammatory change in the interstitial tissue was not so marked on this side as it was on the left

Aorta Showed early lipid deposits in the subintimal tissue

Coronary artery Showed slight change in the intima with endothelial and fibroblastic proliferation and some lipid deposits

Pharyngeal and Faucial tonsils Showed marked hyperplasia of the lymphoid tissue, accumulation of exudate in the crypts, and infiltration in the epithelium which consisted of polynuclear cells, plasma cells, and eosinophiles

Lingual tonsil The lingual tonsils were similar to but less extensively involved than the pharyngeal tonsil

*Anatomic Diagnosis* 1 Acute suppurative nasopharyngitis and tonsillitis 2 Acute diffuse myocarditis 3 Parenchymatous degeneration of liver and kidneys 4 Passive hyperemia of lungs, liver, kidneys 5 Acute hyperplasia of spleen and lymphoid follicles of colon, ileum, cervical, mediastinal, pancreatic and mesenteric lymph nodes 6 Hypertrophy of heart—slight 7 Primary tuberculous focus, upper lobe of left lung, obsolete Fibrous pleural and peritoneal adhesions Remote appendectomy Persistent thymus

It is unfortunate that no electrocardiograms were obtained from the patient just described The clinician had observed a man with acute tonsillitis who, in vivo, presented no sign or symptom pointing towards a cardiac disorder This one case has great significance It demonstrates that acute myocarditis may follow acute tonsillitis Since much electrocardiographic evidence has been collected to show that myocardial disturbances are not at all rare in acute tonsillitis, it is not unsafe to assume that these electrocardiographic alterations actually are due to an acute myocarditis Sudden death or cardiac decompensation following tonsillitis is rare It is reasonable, then, to assume that the vast majority of the cases of acute myocarditis following tonsillitis recover completely This is borne out by the observations of the electrocardiographic changes which show that they most often return to normal A few may heal and retain permanent evidence of a previous myocarditis as shown by some permanent abnormal electrocardiographic alteration

Saphir<sup>15</sup> found acute myocarditis in 19 cases of bronchopneumonia and seven cases of lobar pneumonia Stone, quoted by Fishberg,<sup>16</sup> observed parenchymatous, fatty or hyaline degeneration or cellular infiltration in 79.3 per cent of his necropsies Fishberg points out that Master, Romanoff and Jaffe detected electrocardiographic changes in over 93 per cent of 45 patients with lobar pneumonia and that De Graff, Travell, and Yager, taking less frequent records, found electrocardiographic abnormalities in about one quarter of 975 cases The changes, almost always transitory, included prolongation of the P-R interval, abnormalities of the RT transition, flat, inverted and large T waves, intraventricular block Master and his associates demonstrated changes in the R-T interval that apparently simulated those seen in coronary disease In 78 per cent of the cases it was shown that the

electrocardiographic changes appeared after the temperature dropped to normal

In our series, case 3 (acute myocarditis following a primary atypical pneumonia) showed a complete A-V dissociation, then a normal rhythm with a prolonged P-R interval; and finally a normal tracing. Case 2 (acute myocarditis associated with lobar pneumonia) showed a bundle branch block which persisted for 96 days and was still present when the man was transferred.

Saphir,<sup>17</sup> in his article on Myocarditis in Bronchiectasis, quotes Brody and Smith who found myocardial involvement in 90 per cent of 44 hearts of patients dying from scarlet fever. Case 4 demonstrates electrocardiographic alterations in a patient with scarlet fever myocarditis.

Isolated involvement of the myocardium in gonococcal infection is rare, according to Saphir. The lesions are, for the most part, foci of acute myocarditis and foci of necrosis. The inflammatory process is thought to occur as the result of direct extension into the myocardium from endocardial or valvular lesions. Bang<sup>18</sup> reported six cases of gonorrheal myocarditis diagnosed by electrocardiographic alterations in the course of the disease. Five cases were associated with acute recurrent gonococcal arthritis. One case was an acute gonococcal arthritis following an acute specific urethritis. Bang quotes Dittrick, who reported two instances of isolated myocarditis complicating gonococcal arthritis, showing tachycardia and arrhythmia. Bang also collected a case reported by Guldberg in 1935. He found no other references in the literature. Logue and Hanson<sup>19</sup> found eight cases of heart block among 530 cases of sulfonamide-resistant gonorrhea. They stated that the cause of heart block in this group is not clear. It is likely that they were instances of myocarditis. Of the three cases of gonococcal myocarditis which we observed, Case 5 was associated with a recurrent gonococcal arthritis whereas cases 6 and 7 were associated with a first attack.

Infection of the urinary tract may be the cause of an acute myocarditis. Saphir found four such instances in his study. Case 8 illustrates an acute myocarditis, secondary to a urinary tract infection as evidenced clinically by a tachycardia, and electrocardiographically by tracings showing myocardial damage.

We encountered one case of infectious mononucleosis (case 9) with evidence of myocarditis. Logue and Hanson found in their study one case of infectious mononucleosis with first degree heart block.



Acute myocarditis occurs secondary to many diseases of bacterial or virus origin and to some conditions of undetermined etiology. The myocardial lesions may result either from direct invasion of the heart by the offending organism or from toxins circulating through the blood stream. The following incomplete list mentions some of the conditions in which acute myocarditis has been demonstrated at autopsy: rheumatic fever, diphtheria, typhoid fever, paratyphoid fever, typhus fever, dysentery, mumps, pneumonia, scarlet fever, meningococcus infection, gonococcal infection, tularemia, acute bacterial endocarditis, streptococcal and pneumococcal meningitis, tuberculosis, pyelitis, acute glomerular nephritis, pyemia, subacute bacterial endocarditis (Saphir<sup>15</sup>), purulent otitis media, conjunctivitis and stomatitis (Maslow and Lederer<sup>2</sup>), pyoderma (Maxwell and Barrett<sup>3</sup>), bronchiectasis (Saphir<sup>17</sup>), acute suppurative tonsillitis (authors' case).

A special form of myocarditis has been recorded in the literature under the terms idiopathic myocarditis, Fiedler's myocarditis, isolated myocarditis, interstitial myocarditis, acute or subacute productive myocarditis, fibrous myocarditis. Under the microscope it cannot be differentiated from other types of acute non-specific myocarditis. The diagnosis is usually made after autopsy. This group of myocarditis has the distinction of being classified separately because no evidence of a primary disease is demonstrable at autopsy. This is far from saying that there was no primary infectious agent.

According to Karsner,<sup>20</sup> the differentiation between acute parenchymatous and acute interstitial myocarditis does not seem justifiable. An acute myocarditis may become subacute or chronic, based arbitrarily on duration. Englehardt and Bruno<sup>8</sup> recorded a case of Fiedler's myocarditis in which decompensation occurred over a period of 21 months. Smith and Stephens<sup>10</sup> observed cases of decompensation due to interstitial myocarditis whose clinical course ran several months to two years. Several classifications of myocarditis have been offered on the basis of pathology. Saphir<sup>1</sup> has presented his own classification and discussed those of Brown and Hunt, of Vischer, and of Marshall. We prefer the classification of Marshall, with the modification that isolated myocarditis be grouped not as a specific entity, but as a sub-group of non-specific myocarditis. A modified classification of infectious myocarditis may be stated as follows:

#### INFECTIOUS MYOCARDITIS

- 1 Specific myocarditis (Rheumatic, tuberculous, syphilitic)
- 2 Non-specific myocarditis
  - (a) Known etiology — (Diphtheria, tonsillitis, typhus fever, bronchiectasis, etc. or clinical entity of undetermined etiology such as infectious mononucleosis)
  - (b) Unknown etiology — Fiedler's myocarditis
- (3) Septic myocarditis in septicemia and in association with subacute bacterial endocarditis

Fetal myocarditis is included by Saphir as a separate group, but with some question as to its occurrence. Only a few references appear on this con-

dition in the older literature in connection with observations on congenital heart disease, in which intra-uterine cardiac inflammation was suspected as the underlying factor

The classification of acute myocarditis from a clinical standpoint is difficult. In a general way we may find the following groups which show

- 1 Signs
- 2 Symptoms
- 3 Signs and symptoms
- 4 Neither signs nor symptoms

The signs and symptoms of acute myocarditis have been well discussed elsewhere<sup>11, 21</sup>. Angina pectoris, palpitation, breathlessness, asthenia, arrhythmia, and gallop rhythm following acute infection have been noted. Left or right ventricular failure, or both, may occur as a result of myocardial insufficiency.

The criteria for diagnosis of acute myocarditis as set down in the publication of the New York Heart Association<sup>22</sup> may be followed. The diagnosis can be made correctly more often than it is. The first requisite for recognition of the condition is the appreciation that acute myocarditis is not a rare complication of infectious disease, acute or chronic. Patients, whose convalescence from acute infection is slow and who complain of profound asthenia after the acute disease has apparently subsided, should be examined carefully for evidence of myocarditis. The symptoms of slight precordial discomfort, angina pectoris, or breathlessness associated with or occurring shortly after the termination of an acute infectious disease, should be regarded with suspicion. Arrhythmias and gallop rhythm should be thoroughly investigated. A persistently rapid sedimentation rate after the primary infectious disease process has subsided should likewise make the physician study his patient carefully for a possible complicating myocarditis.

There is a group of patients who develop myocarditis after an infectious disease and show no arrhythmias, no symptoms referable to the heart and in whom the electrocardiogram may or may not reveal evidence of myocardial disease. Schei f and Boyd<sup>11</sup> have pointed out that alterations of the electrocardiogram are not evident in every case nor continually in the positive ones. It is to this group that more attention should be directed. Until our present knowledge of physical diagnosis is more advanced, or perhaps more wisely utilized, the diagnosis of myocarditis in these individuals will rest mainly with the demonstration of myocardial involvement by means of the electrocardiogram and often by repeated electrocardiograms.

The significance of electrocardiographic abnormalities in the diagnosis of acute non-specific myocarditis is not fully recognized. This is indeed strange. In the course of acute rheumatic fever, electrocardiographic alterations such as profound arrhythmias and T-wave changes are accepted as unequivocal evidence of disease of the myocardium. In the course of acute rheumatic fever, in a goodly number, the electrocardiographic changes

are reversible and may return to normal. When this sequence of events has occurred, the clinical interpretation is readily made that the pathologic process responsible for the particular change has resolved. Is there, then, any logical reason to assume that similar observations as to arrhythmias and T-wave changes, which occur in the course of other acute infectious disease in which non-specific myocarditis has been shown to occur, do not represent evidence of myocarditis? And when the electrocardiographic alterations in non-specific myocarditis return to normal, should it not likewise be interpreted that the inflammatory process responsible for the particular alterations has subsided? When the electrocardiographic change has become permanent, it is most likely that a permanent change has occurred in the myocardium.

As far as prognosis is concerned, most cases recover. Some die suddenly<sup>6, 17</sup>. Some show cardiac decompensation terminating in death<sup>4, 10</sup>. Saphir<sup>17</sup> recorded eight cases of bronchiectasis with myocarditis of which three died suddenly. In another paper he refers to Lisa, who reviewed the autopsies of 41 patients dying suddenly and found evidence of acute myocarditis in 36 cases<sup>1</sup>. From these observations one can conclude that when sudden death occurs in any disease associated with infection, the myocardium should be studied with great care to determine whether or not myocarditis is present.

The scheme which follows indicates the possible course of acute non-specific myocarditis of infectious origin. Acute non-specific myocarditis is always secondary to a primary disease of

- |                     |   |
|---------------------|---|
| I Known etiology    | (such as typhus fever, acute tonsillitis, etc., or of a recognizable entity such as infectious mononucleosis), with the result that the following takes place |
|                     | (a) Recovery—Majority   |
|                     | (b) Death —Minority   |
|                     | 1 Sudden  |
|                     | 2 With cardiac decompensation   |
| II Unknown etiology | with the result that the following takes place  |
|                     | (a) Recovery—Majority—(as evidenced by electrocardiographic alterations with no history of antecedent disease)  |
|                     | (b) Death —Minority—(Fiedler's myocarditis)   |
|                     | 1 Sudden  |
|                     | 2 With cardiac decompensation   |

The treatment of myocarditis is symptomatic. Initially, bed rest is most important. The clinical signs, electrocardiographic changes, and the erythrocyte sedimentation rate should be used as criteria for the duration of the period of rest.

### DISCUSSION

The frequency of myocarditis has been stressed by a few clinicians and a few pathologists. Saphir, Wile and Reingold<sup>23</sup> found evidence of myocardial inflammation in 6.83 per cent of 1,420 autopsies on children. They encountered the same condition in 4.05 per cent of autopsies on 3,712 adults.

during the same period. They state that the clinician diagnoses myocarditis rarely and the pathologist finds it more frequently. We agree that the clinician diagnoses it rarely, but if all the evidence in the literature on electrocardiographic changes in the course of acute or chronic infections be taken as evidence of an acute inflammatory process involving the myocardium (and we believe it is such evidence), the statement should be modified to say that the clinician finds it frequently, more frequently than the pathologist, but diagnoses it rarely. The reasons for the failure of clinicians to make such diagnoses have been mentioned above. We have apparently grown up in a period of medicine, in which the term myocarditis has fallen into profound disrepute.

It is probable that the incidence of myocarditis found at autopsy will be even greater when more care is taken by the pathologist in demonstrating the condition. Saphir has recommended taking many sections from the myocardium and examining them most carefully. Since acute myocarditis may involve the myocardium focally as well as diffusely, one or two sections cut by the microtome even from several blocks of tissue represent an infinitesimally small exploration of a relatively vast mass.

Aschoff nodules are found in only 80 per cent of cases in which acute myocarditis is demonstrated in hearts bearing the stigmata of rheumatic heart disease.<sup>27-28</sup> In the 20 per cent in which no specific lesions are found, it appears necessary that the pathologic changes be more carefully evaluated. If there is no evidence of recent valvulitis, no evidence of proliferative changes in the endothelium of the smaller vessels, no evidence of Aschoff nodules elsewhere in the body, the diagnosis of rheumatic myocarditis should be made with caution. There is no reason to suppose that a rheumatic heart is immune to acute non-specific myocarditis. From a clinical standpoint, it is not rare following an acute upper respiratory tract infection to observe acute decompensation in a patient who previously had never decompensated or whose decompensation had been well controlled by therapy.

A correct appraisal of acute myocarditis is important. How frequently it occurs is not known. We are inclined to agree with Scherf and Boyd<sup>11</sup> who venture the assertion that with the frequency of infectious diseases and miscellaneous infections such as tonsillitis, etc., there are but few individuals who at some time or other do not have small inflammatory myocardial foci. If this is found to be so, myocarditis will have to be reevaluated as one of the most common affections of the heart.

The frequency of the occurrence of acute myocarditis is not taken into consideration as much as it should be by investigators interested in establishing normal values for characteristics of the electrocardiogram. In a study of 100 cases of a prolonged P-R interval Logue and Hanson<sup>12</sup> found 19 cases with no disease evident. They stated in summary that an occasional person may have a prolonged conduction time which is normal for that person. Graybiel et al.<sup>13</sup> found 10 instances among 1000 aviators of a P-R interval greater than 0.21 second. They stated that although P-R

intervals greater than 0.20 second should raise the question of past or present heart disease, they may indicate neither. Stewart and Manning<sup>27</sup> found 2.2 per cent of 500 healthy aviators with P-R intervals greater than 0.21 second in Lead II and 0.6 per cent greater than 0.24 second. They concluded that this number of normal males may be expected to have P-R intervals greater than 0.20 second. They also stated that this does not prove that they will not develop disease at a later time. At this point it must again be emphasized that prolongation of the P-R interval is a common abnormality seen in the course of many acute infectious diseases. This is commonly accepted as evidence of acute myocarditis when it is observed during acute rheumatic fever. It is likewise evidence of myocarditis in other infectious diseases. Prolongation of the P-R interval is reversible in many instances. In others it becomes a permanent characteristic. Where it is permanent, it is believed that some fibrosis has occurred along the conduction pathways. Since most of these instances of acute myocarditis are not recognized clinically, an observer taking routine electrocardiograms will collect a number of cases of prolonged P-R interval in apparently healthy individuals. The observers will naturally assume that these are normal variations. It is thus evident that a collection of cases studied statistically for P-R interval values may contain an internal bias. An alternate conclusion from the studies mentioned above might be that an abnormal atrio-ventricular conduction as evidenced by a prolonged P-R interval may be due to previous disease but is compatible with good cardiac function, as far as we know.

Weinstein<sup>28</sup> published 10 cases of "*Atypical*" *Coronary Disease in Young People* and emphasized the presence of antecedent acute infections. He invoked the possibility of a coronary arteritis as the underlying pathologic factor. In nine of the 10 cases the acute cardiac symptoms for which the patients were admitted followed from four days to several weeks after an acute infection. Five followed a "throat infection." Two followed "tonsillitis." One followed an "upper respiratory" infection. One followed a "pharyngitis." The precordial pain, electrocardiographic alterations and rapid erythrocyte sedimentation rate are phenomena also seen in acute myocarditis. The electrocardiographic patterns seen in anterior and posterior wall infarctions following coronary artery thrombosis are not pathognomonic of the underlying atherosclerotic process. Conclusions concerning the type of cardiac disease present cannot be drawn from the electrocardiogram alone.<sup>29</sup> It is thus possible that some of the cases reported as "atypical" coronary disease were in reality cases of acute myocarditis.

Scherf and Boyd<sup>31</sup> point out that occasionally in older patients it may be difficult to decide whether or not myocardial damage seen in the electrocardiogram is evidence of an old myocarditis, or secondary to coronary sclerosis. We have seen diagnoses made of acute rheumatic fever on patients without joint manifestations and without evidence of valvulitis, who had a continued fever and electrocardiographic findings of a prolonged P-R

interval The electrocardiographic changes were interpreted as due to a myocarditis, which was reasonable But the clinician failed to realize that a prolonged P-R interval due to myocarditis can exist outside of acute rheumatic fever

### SUMMARY

Eleven cases of acute myocarditis, non-specific in nature, have been presented The studies are entirely clinical The reasons for the diagnoses are presented Evidence is shown that myocarditis occurs more frequently than has been supposed Some of the reasons for failure to recognize the condition are indicated Acute myocarditis is discussed The importance of a better understanding and a wider appreciation of acute non-specific myocarditis is stressed It is pointed out that failure to appreciate the frequency of myocarditis may affect adversely some of the current research

A case of acute myocarditis, following acute suppurative tonsillitis and eventuating in death, is described As far as we know, this is the first case on record (proved by autopsy) of acute non-specific myocarditis following acute tonsillitis

### CONCLUSIONS

- 1 Acute non-specific myocarditis occurs more often than is generally appreciated
- 2 The clinical diagnosis can be made more frequently than it is
- 3 Acute non-specific myocarditis can follow acute suppurative tonsillitis
- 4 Acute non-specific myocarditis was observed clinically in peritonsillar abscess, pneumonia, scarlet fever, gonococcal arthritis, urinary tract infection, infectious mononucleosis and typhus fever

### BIBLIOGRAPHY

- 1 SAPHIR, OTTO Myocarditis A general review with an analysis of 240 cases, *Arch Path*, 1941, **xxii**, 1000-1051
- 2 MASLOW, H L, and LEDERER, MAX Interstitial myocarditis in a child 19 months of age, *Am Jr Dis Child*, 1943, **xlv**, 801-814
- 3 MAXWELL, E S, and BARRETT, C C Acute interstitial myocarditis. Report of a case following a severe dermatitis due to sulphur ointment, *Arch Dermat and Syph*, 1934, **xxix**, 382-386
- 4 SIMON, M A, and WOLPAU, SIDNEY Acute, subacute and chronic isolated myocarditis Report of a case, *Arch Int Med*, 1935, **lvi**, 1136-1142
- 5 HANSMANN, G H, and SCHENCKEN, J R Acute isolated myocarditis Report of a case, with a study of the development of the lesion, *Am Heart Jr*, 1938, **xv**, 749-756
- 6 HELWIG, F C, and WILHELMY, E W Sudden and unexpected death from acute interstitial myocarditis A report of three cases, *Ann Int Med*, 1939, **xiii**, 107.
- 7 GREFENBAUM, J V, FELSON, W, and ZELIGS, M Acute interstitial myocarditis in an infant Report of a case with autopsy findings, *Jr Pediat*, 1941, **xviii**, 799-804
- 8 ENGLEHARDT, H T, and BRUNO, F E Fiedler's myocarditis, report of a case, *New England Jr Med*, 1943, **ccxxviii**, 222-224
- 9 COLLIER, W W, and MARCONE, PETER Acute isolated myocarditis, case report, *Am Jr Clin Path*, 1944, **xiv**, 399-404

- 10 SMITH, FRED M, and STEPHENS, R L Acute, subacute, and chronic interstitial myocarditis Report of six cases, *Trans Assoc Am Phys*, 1938, lxi, 120-128
- 11 SCHERF, DAVID, and BOYD, L J Cardiovascular diseases, 1939, The C V Mosby Co, St Louis, pp 176-180
- 12 MAHER, C C, and WOSIKA, P H Electrocardiography, 3rd Edition, 1940, Williams and Wilkins Co, Baltimore, p 297
- 13 SCHERF, DAVID Myocarditis, following acute tonsillitis, *The New York Medical College and Flower Hospital Bulletin* No 13, Dec 1940, pp 252-260
- 14 CARR, J G, and WALSH, J A Acute infectious myocarditis, *Illinois Med Jr*, 1934, lxxv, 134-137
- 15 SAPHIR, OTTO Myocarditis A general review with an analysis of 240 cases, *Arch Path*, 1942, xxxiii, 88-137
- 16 FISHBERG, A M Heart failure, 2nd Edition, 1940, Lea and Febiger, Philadelphia, p 664
- 17 SAPHIR, OTTO Myocarditis in bronchiectasis, *Arch Int. Med*, 1943, lxxii, 775-781
- 18 BANG, O Gonorrheal myocarditis, *Brit. Med Jr*, 1940, 117-120
- 19 LOGUE, R B, and HANSON, J F Heart block a study of 100 cases with prolonged P-R interval, *Am Jr Med Sci*, 1944, ccvii, 867
- 20 KARSNER, H T Human pathology, 6th Edition, 1942, J B Lippincott Company, Philadelphia, p 372
- 21 CECIL, R L A textbook of medicine, 5th Edition, 1942, W B Saunders Co, Philadelphia, pp 1169-1173
- 22 NEW YORK HEART ASSOCIATION Nomenclature and criteria for diagnosis of diseases of the heart, 4th Edition, 1942, pp 47-48
- 23 SAPHIR, O, WILE, S A, and REINGOLD, I M Myocarditis in children, *Am Jr Dis Child*, 1944, lxxvii, 294-312
- 24 BOYD, WILLIAM A textbook of pathology, 4th Edition, 1943, Lea and Febiger, Philadelphia, p 351
- 25 BELL, E T A textbook of pathology, 4th Edition, 1941, Lea and Febiger, Philadelphia, p 53
- 26 GRAYBIEL, A, MCFARLAND, R A, and GATES, D C Analysis of the electrocardiograms obtained from 1000 young healthy aviators, *Am Heart Jr*, 1944, xxvii, 524-549
- 27 STEWART, C B, and MANNING, G W A detailed analysis of the electrocardiograms of 500 RCAF aircrews, *Am Heart Jr*, 1944, xxvii, 502-523
- 28 WEINSTEIN, JOSEPH "Atypical" coronary disease in young people, *Ann Int. Med*, 1944, xxi, 252-271
- 29 SCHERF, DAVID, and BOYD, L J Clinical electrocardiography, 1940, The C V Mosby Company, St Louis, p 53 and p 99

# MENINGOCOCCIC MENINGITIS TREATED WITH SULFADIAZINE AND SULFAMERAZINE: A THREE YEAR STUDY\*

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MENINGOCOCCIC meningitis has been encountered with considerable frequency in the Gallinger Municipal Hospital as well as throughout the United States during the past few years. Previous reports from this clinic<sup>1,2</sup> and from others<sup>3,4,5,6</sup> have amply demonstrated the suitability of sulfadiazine and sulfamerazine for the treatment of this type of infection. The number of patients reported in each of these studies has been relatively small, however, or the period of time covered by them has been short. It still is pertinent to question the efficacy of these drugs when used in large numbers of patients treated over a longer period of time, and to study the factors which influence the prognosis in these patients.

In the present paper our purpose is to evaluate our results in the treatment of 207 patients with meningococcic meningitis who have been treated over a period of three years, between October 20, 1941, and October 31, 1944.

## PROCEDURE

Routine procedures in the diagnosis and treatment of these patients have been carried out as follows. As soon as a patient believed to have meningitis was admitted to the ward, a lumbar puncture was performed. On the specimen of spinal fluid obtained several examinations were made immediately. A cell count and a Pandy test were done. Smears of the centrifuged sediment were made. They were stained with both methylene blue and Gram's stains. If organisms believed to be meningococci were seen, typing by means of the Neufeld technic was attempted. Cultures were planted in tryptose-phosphate or tryptose-phosphate-hemoglobin broth and on chocolate agar slants. A quantitative dextrose determination was made on the clear supernatant fluid by an application of Benedict's modification of the Folin-Wu method.<sup>7</sup> After this study had established a presumptive diagnosis of meningococcic meningitis and a blood culture had been obtained, treatment was begun. An initial oral dose of 6 grams of sulfadiazine or sulfamerazine was followed by 1 gram every four hours in adults. A proportionately smaller dose was given to children. For severely ill patients, especially those too stuporous to swallow, or for those who were vomiting excessively, the initial

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dose and a varying number of subsequent doses were given as a 0.5 to 1 per cent solution of the sodium salt of the drug intravenously or subcutaneously. The sulfonamide drug was continued until the patient was afebrile for approximately seven days unless some indication for stopping the drug developed sooner. Frequent hemograms, urinalyses and blood urea nitrogen and blood sulfonamide determinations were obtained during the period of drug administration. Follow-up lumbar punctures were done on the second hospital day and again when discharge was contemplated. If the cell count had not fallen to 30 cells per cubic millimeter the puncture was repeated at weekly intervals until the level was reached. At this time the patient was allowed out of bed and was subsequently discharged. Additional lumbar punctures were done only when the course of the disease was not progressing satisfactorily. Each spinal fluid specimen was examined in the same way as the one obtained by the initial lumbar puncture.

Patients who responded poorly to this régime in the first 24 to 48 hours were considered candidates for serum therapy, or, during 1944, for penicillin. After reevaluation of the clinical status of the patient and the laboratory findings, serum was given intravenously if it was believed indicated. Penicillin was administered intrathecally in doses of 10,000 to 20,000 units. This was adjusted to a concentration of 1,000 units per cubic centimeter. The volume of diluted penicillin given always was 5 to 10 cubic centimeters less than the amount of cerebrospinal fluid withdrawn. The penicillin dose was repeated every 12 to 24 hours until satisfactory improvement was noted.

There was a total of 207 patients with meningococcic meningitis treated by this technic. The etiologic agent in every case was established by one or more of the following methods: (1) positive spinal fluid culture, (2) a positive blood culture in a patient with meningitis, or (3) a smear containing typical gram negative intracellular or extracellular diplococci. All cases of meningitis fulfilling these criteria were included in the present study and all others excluded. Patients with meningococcemia without meningitis were likewise omitted.

Meningococci were demonstrated in the stained sediment of the original specimen of cerebrospinal fluid from 188 (90.8 per cent) of our patients. They were present in sufficient numbers to make the diagnosis by means of the stained film alone quite certain in 134 patients, and to make it very probable in 54 patients. In many instances the diagnosis was confirmed immediately by direct Neufeld typing from the spinal fluid sediment. Whenever possible, the organisms were typed.\* Among the 146 cases in which typing was successful, there were 136 patients with Group I, and 10 with Group IIa meningococcic infections.

### RESULTS

From table 1 it will be seen that 21 (10.1 per cent) of the 207 patients died. The case-fatality rate varied widely according to the age of the pa-

\* We wish to thank Dr. Sara E. Branham of the National Institute of Health for typing many of these organisms.

TABLE I

Effect of the Age of the Patient and the Presence of Coma or Delirium Upon the Outcome in 207 Patients with Meningococcic Meningitis

| Age   | Total Patients Treated |        |          | Patients Admitted in Coma |   |        |          |
|-------|------------------------|--------|----------|---------------------------|---|--------|----------|
|       | Number Treated         | Died   |          | Number                    | Per Cent of Total Patients in the Age Group | Died   |          |
|       |                        | Number | Per Cent |                           |   | Number | Per Cent |
| Total | 207                    | 21     | 10.1     | 94                        | 45.4  | 20     | 21.3     |
| 0-9   | 31                     | 0      | 0        | 5                         | 16.1  | 0      | 0        |
| 10-19 | 37                     | 2      | 5.4      | 20                        | 54.1  | 1      | 5.0      |
| 20-29 | 43                     | 4      | 9.3      | 19                        | 44.2  | 4      | 21.1     |
| 30-39 | 46                     | 3      | 6.5      | 16                        | 34.8  | 3      | 18.8     |
| 40-49 | 20                     | 4      | 20.0     | 12                        | 60.0  | 4      | 33.3     |
| 50-59 | 19                     | 6      | 31.6     | 14                        | 73.7  | 6      | 42.9     |
| 60-70 | 11                     | 2      | 18.2     | 8                         | 72.7  | 2      | 25.0     |

patient. In general it fell into one of three groups. Among patients nine years of age or less, there were no deaths. This is explained partly by our good fortune in not encountering any fulminating infections with the Waterhouse-Friderichsen syndrome in this age-group and secondly by the fact that there were only 10 children who were less than two years old. Our youngest patients were four, eight, eight and 10 months respectively. Six patients were in the second year of life. None of these very young patients was in coma at the time of entry.

The second group comprised patients in the second, third and fourth decades, in whom the case-fatality rate varied from 5.4 to 9.3 per cent. The third group included patients 40 years of age and over. The death rate for the whole group was 24 per cent and varied from 18 to 32 per cent. The relatively low percentage of deaths in the seventh decade can undoubtedly be explained on the basis of chance owing to the small size of the group.

In addition to age, the other important factor which greatly affected the outcome was the presence of coma or delirium. The death rate among the 94 patients with coma or delirium on admission was 21.3 per cent, whereas among the 113 patients who did not exhibit these manifestations only one patient (0.9 per cent) died. This patient was a girl of 15 years, suffering from a fulminating infection with the Waterhouse-Friderichsen syndrome, who died four hours after entry. Furthermore, among the 31 patients who had been in coma for 24 hours or longer before specific treatment was begun, 11 died resulting in a still higher case-fatality rate (35.5 per cent).

In general, coma or delirium tended to be present more frequently among patients in the older age-groups, and the mortality rate in patients with coma or delirium rose progressively with age. Thus, the higher case-fatality rates in older patients might be explained partly by the higher incidence of coma or delirium, but they probably were also due in part to other and yet unknown factors that cause older patients to respond less well than do their younger co-sufferers.

Other findings of some prognostic significance were the presence, in the initial specimen of spinal fluid examined, (1) of dextrose in a concentration less than 10 milligrams per 100 cubic centimeters, or (2) of a large number of meningococci in the sediment after centrifugation. Among comatose or delirious patients with either or both of the above findings (table 2), the

TABLE II

The Effect of Delirium or Coma on Admission and of Many Cocci and/or Dextrose Levels below 10 Milligrams per 100 Cubic Centimeters in the Initial Specimen of Cerebrospinal Fluid on the Prognosis in 207 Patients with Meningococcic Meningitis

|   | Patients Treated | Patients Died |          |
|---|------------------|---------------|----------|
|   |                  | Number        | Per Cent |
| Total Patients                                    | 207              | 21            | 10.1     |
| Patients Rational on Admission                    | 113              | 1             | 0.9      |
| Total Patients with Coma or Delirium on Admission | 94               | 20            | 21.3     |
| Many Cocci,* Dextrose below 10                    | 28               | 7             | 25.0     |
| Many Cocci,* Dextrose 10 or above                 | 15               | 4             | 26.7     |
| Few Cocci or less,† Dextrose below 10             | 24               | 6             | 25.0     |
| Few Cocci or less,† Dextrose 10 or above          | 27               | 3             | 11.1     |
| Total Many Cocci *                                | 43               | 11            | 25.6     |
| Total Dextrose below 10                           | 39               | 10            | 25.6     |

\* Many cocci were recorded when at least one organism was seen in practically every field, and several organisms were seen in most fields.

† Few cocci were recorded when half of the fields contained no organisms, and relatively few organisms were present in any single field.

case-fatality rate was 25 per cent, whereas among 27 comatose or delirious patients in whose initial spinal fluids the dextrose level was above 10 milligrams per 100 cubic centimeters and organisms were few or absent, there were only three (11 per cent) who died.

The present series of cases confirms our previous observation that neither the presence nor absence of petechiae or of bacteremia, nor the height of the leukocyte count in the spinal fluid has any bearing upon prognosis in sulfonamide-treated patients.

### COMPLICATIONS

Among the patients who recovered, the most frequent complications related to the infection were nerve palsies. These occurred in 35 patients. The majority of the palsies were present on admission or when they could be identified after a comatose patient regained consciousness. They involved both sensory and motor nerves. The most frequent sensory change noted was deafness which was present in some degree in 10 patients. In one of these, a child, deafness became apparent approximately one week after the patient had been discharged in what was thought to be good condition. In

one patient there was involvement of the fifth cranial (trigeminal) nerve with sensory changes in the face. Motor nerves were involved in 23 patients. These included the third (oculomotor), fourth (trochlear), sixth (abducens), seventh (facial), eleventh (spinal accessory) and twelfth (hypoglossal) cranial nerves. In one boy there was a temporary spinal nerve palsy resulting in a transitory foot drop. More nerves than one were frequently involved, the greatest number in any one patient being six. Although follow-up examinations of patients with nerve palsies have not been complete we have noted that little or no recovery occurred in a large majority of the patients who became deaf, whereas we have seen no patient with a motor nerve palsy that persisted for longer than six months after the onset of meningitis.

The other complications that we have encountered include 10 instances of arthritis or tenosynovitis and four of purulent conjunctivitis. All of these complications have been of short duration with no residual manifestations. In addition, one elderly patient developed extensive thrombophlebitis with secondary cerebral emboli and permanent mental deterioration.

#### TREATMENT

The basic treatment for all types of purulent meningitis is identical. This consists of (1) adequate sedation to keep the patient quiet and comfortable, (2) hydration, (3) sulfonamides and (4) nursing care. In our hands, morphine in full dosage has been the sedative of choice. It is the only sedative that will relieve the severe head pain suffered by these patients and thereby bring rest. Of equal importance is the adequate hydration of the patient. Practically all patients with meningitis are dehydrated from fever, vomiting, and failure to take fluids. It is of utmost importance to rehydrate the patients, that is to restore their fluid and electrolyte balance as rapidly as possible. It is important that the sulfonamide drugs be given well diluted so that the kidneys will be able to eliminate them without calculus formation. If the drugs are given parenterally, the initial dose should be in a concentration of 0.5 per cent or less.

The main specific therapeutic agent in all of our patients has been one of the sulfonamide compounds. Sulfadiazine was used for 112 patients of whom 13 (11.6 per cent) died. Sulfamerazine was used for 95 patients of whom eight (8.4 per cent) died. Two patients who were treated with sulfamerazine suffered clinical relapses while in the hospital. One patient, a female aged eight months, was treated again with a good response. The infant left the hospital in good condition. The other patient, a negro male aged 41 years, maintained a fever for 13 days after admission. No cause for the fever could be found and the spinal fluid showed only moderate abnormality. The sulfamerazine was discontinued and, since the patient became afebrile, it was thought that the episode had been drug fever. One week later, however, the temperature rose again and the patient showed a

pleocytosis of 4,000 cells in the spinal fluid. A test dose of sulfamerazine caused a sharp rise in temperature. The temperature remained elevated for 24 hours during which sulfadiazine was administered. Thereafter the patient was treated with sulfathiazole to which he made a slow but satisfactory response. A third patient, a white female aged 34, developed a toxic rash and fever after two days of sulfamerazine therapy. She then was given sulfadiazine to which she showed sensitivity reactions after four days. Her clinical condition was satisfactory and all specific medication was discontinued at that time.

Because some investigators have advocated that very high concentrations of sulfonamides be maintained in the blood, we have studied the relationship of the blood sulfonamide levels to recovery (table 3). Among 186 patients

TABLE III

Blood Concentration of Sulfadiazine or Sulfamerazine at Certain Times during the Course of Meningococcic Meningitis

| Concentration of Sulfonamide in Blood<br>Mg Per Cent | Number of Patients Showing the Indicated Blood Concentration |                                |               |       |
|--|--|--------------------------------|---------------|-------|
|  | Concentration on the Day the Temperature Became Normal       | Maximum Concentration Observed |               |       |
|  |  | Patients Lived                 | Patients Died | Total |
| 0-4.9  | 27   | 2                              | 1             | 3     |
| 5.0-9.9  | 64   | 43                             | 2             | 45    |
| 10.0-14.9  | 48   | 61                             | 3             | 64    |
| 15.0-19.9  | 15   | 43                             | 4             | 47    |
| 20.0-24.9  | 6  | 18                             | 1             | 19    |
| 25.0-29.9  | 3  | 11                             | 2             | 13    |
| 30.0-34.9  | 0  | 4                              | 0             | 4     |
| 35.0-39.9  | 0  | 1                              | 0             | 1     |
| No Record  | 23   | 3                              | 8             | 11    |
| Died   | 21   | 0                              | 21            | 21    |
| Total  | 207  | 186                            | 21            | 207   |

who lived, there were 163 on whom sulfonamide levels were determined on the day the patient became afebrile. It is of great interest to note that 27 patients had levels of less than 5 milligrams per 100 cubic centimeters on that day. The lowest level so recorded was 1.6 milligrams per 100 cubic centimeters, and three patients had levels below 3.0 milligrams per 100 cubic centimeters. A total of 91 patients, almost 50 per cent of the patients who survived, had blood levels of less than 10 milligrams per 100 cubic centimeters, and only 24 had levels of 15.0 milligrams or above on the day their fever subsided.

The maximum blood levels obtained on each patient also have been tabulated. For two patients who lived and for one who died, the maximum level was below 5.0 milligrams per 100 cubic centimeters. Maximum levels below 10 milligrams per 100 cubic centimeters were found in 45 patients, maximum concentrations from 11 to 20 milligrams in 104 patients, and concentrations of above 20.0 milligrams in only 34 patients who recovered. The

relative frequency of the various maximum blood levels in patients who died was approximately the same as those obtained in patients who recovered

This evidence confirms our point of view that it is not necessary to increase the dose of sulfonamides in order to obtain an arbitrary concentration in the blood as long as the patient's response is satisfactory. Furthermore, since toxic manifestations, especially renal calculi, are more frequently encountered when high concentrations of sulfonamides are present, it is not desirable to raise the dosage of these drugs unless it becomes necessary.

The toxic manifestations related to the administration of sulfonamide compounds have been comparable in every way to those reported elsewhere,<sup>2, 8, 9</sup> and need not be reviewed here

Other specific therapy that has been used has been the administration of antimeningococcic serum or of penicillin. Serum was used occasionally in 1942 and 1943, being given to 11 patients. Two patients received serum, one intravenously and one intrathecally, in other hospitals before being transferred to Gallinger. The course of these two patients was in no way different from patients who received no serum. One patient who was admitted in diabetic acidosis was given serum as soon as the administration of the initial dose of sodium sulfadiazine was completed. The patient died within eight hours. Eight other patients received serum after having failed to respond to sulfonamide therapy in the first 24 to 48 hours. Four of these continued to fail and died. In two patients recovery definitely seemed to be related to the administration of serum, in that prompt improvement followed. In the other two patients who recovered, the actual value of the serum in influencing the outcome is questionable. Four of the six patients who survived after receiving serum developed mild serum sickness.

Since January, 1944, penicillin has been used in all patients who have failed to respond satisfactorily to sulfonamide therapy. Only two such patients have been encountered. Both were males, aged 47 and 41 respectively, who were in deep coma on admission. The initial cerebrospinal fluid showed many Group I meningococci in both. The dextrose level was less than 5 milligrams per 100 cubic centimeters in the first. It was not recorded in the second. Eighteen hours after admission the first patient had a temperature of 106° F (rectal). He was markedly worse than on admission and was in peripheral vascular collapse. He received 25,000 units of penicillin intrathecally and after eight hours an additional 15,000 units. Thereafter he received 15,000 units intrathecally every 12 hours for a total of five doses. His response was dramatic. Within 24 hours his temperature fell permanently below 102° F, his respirations were regular and much less rapid, and he showed definite improvement. On the third day he began to respond rationally; on the fifth day he became afebrile. Thereafter his convalescence was uneventful.

The second patient also failed progressively but less dramatically. As a result his penicillin was started 34 hours after entry, and only 15,000 units

were given intrathecally. He continued to fail and died eight hours later. In this case the administration of penicillin may have been withheld too long.

### SEASONAL INCIDENCE

Table 4 shows the effect of the time of onset of the disease as the epidemic progressed on the incidence, severity, and recovery. From January 1

TABLE IV  
Comparison of the Seasonal Incidence of Meningitis with the Mortality Rate and the Duration of Illness

| Season of Onset | Total Treated | Died   |          | Average Duration of Fever* (Days) | Average Duration of Pleocytosis Spinalis† (Days) |
|-----------------|---------------|--------|----------|-----------------------------------|--|
|                 |               | Number | Per Cent |                                   |  |
| Jan-June 1942   | 28            | 3      | 10.7     | 1.5                               | 15.7   |
| July-Dec 1942   | 20            | 3      | 15.0     | 3.1                               | 19.8   |
| Total 1942      | 48            | 6      | 12.5     | —                                 | —  |
| Jan-June 1943   | 71            | 7      | 9.9      | 2.9                               | 23.0   |
| July-Dec 1943   | 36            | 6      | 16.7     | 2.4                               | 21.8   |
| Total 1943      | 107           | 13     | 12.1     | —                                 | —  |
| Jan-June 1944   | 42            | 2      | 4.8      | 3.4                               | 20.1   |
| July-Oct 1944   | 9             | 0      | 0.0      | 2.0                               | 14.1   |
| July-Dec 1944   | 19            | 2      | 10.5     | †                                 | †  |
| Total 1944      | 61            | 4      | 6.5      | —                                 | —  |

\* From beginning of sulfonamide therapy until temperature permanently below 101° F (rectal) in patients who recovered only.

† From beginning of sulfonamide therapy until the leukocytes were below 30 per cubic millimeter.

‡ Data not yet available.

to June 30, 1942, there were 28 patients. Fifteen of these were admitted in delirium or coma. There were three (10.7 per cent) deaths. From July 1 to December 31, 1942, there were 20 patients of whom 11 were admitted in delirium or coma. There were three (15 per cent) deaths. From January 1 to June 30, 1943, there were 71 patients of whom 33 were in delirium or coma. There were seven (9.9 per cent) deaths. From July 1 to December 31, 1943, there were 36 patients of whom 15 were in delirium or coma. There were six (16.7 per cent) deaths. From January 1 to June 30, 1944, there were 42 patients of whom 16 were in delirium or coma on admission. There were two (4.8 per cent) deaths. From July 1 to October 31, 1944, there were nine patients of whom three were comatose or delirious. There were no deaths\*. Thus, there was no significant increase or decrease in mortality though there was a downward trend in 1944. It is interesting to note that in every year the mortality rate has been higher in the second half year than in the first half year, though in each instance the number of patients has been greater in the first half year. The rate of recovery as judged by the average duration of fever and of pleocytosis in the spinal fluid

\* From July 1 to December 31, 1944, there were 19 patients with two (10.5 per cent) deaths.

showed a definite prolongation from January 1942 through June 1943, but following that there was a slight but definite decrease in the average length of illness

### COMMENT

In our previous report of 118 patients with meningococcic infections treated with sulfadiazine or sulfamerazine, we commented upon the low fatality rate observed, even though the group contained many patients in whom the prognosis might have been unfavorable. We have now enlarged our series to 207 consecutive patients with meningococcic meningitis treated by the same methods. The fatality rate for the entire group is 10.1 per cent, which is considerably lower than that observed in the presulfonamide days. Although the death rates reported from army and navy hospitals are lower than our figures, the difference is undoubtedly due to the fact that their patients are in a more favorable age-group and their treatment usually is instituted much earlier in the disease.

We have confirmed our earlier finding that the most important single factor in prognosis is the presence or absence of coma or delirium. Among the 113 patients who were rational on admission, only one died and she was suffering from the Waterhouse-Friderichsen syndrome. On the other hand, among 94 patients who were in coma or delirium on admission, 20 (21.3 per cent) died. Furthermore, among 31 patients who had been in coma or delirium for 24 hours or more before treatment was instituted, 11 (35.5 per cent) died. Thus, not only the presence but also the duration of coma is of great importance in determining prognosis in an individual case.

Another important factor in prognosis is the age of the patient. In general, the case fatality rate rose progressively as the age of the patients increased.

Of less significance in prognosis was the number of organisms and the reduction in dextrose in the initial specimen of spinal fluid. When either the number of organisms was high or the sugar was reduced below 10 milligrams per 100 cubic centimeters, the mortality rate in comatose patients was considerably increased. The presence or absence of bacteremia, of petechiae, or of a high leukocyte count in the spinal fluid had no bearing on the prognosis. Furthermore, there was no relationship between the concentration of sulfonamides in the blood and the outcome.

The epidemic of meningococcic meningitis which has been present in the District of Columbia as well as throughout the United States in the past three years has already shown evidences of being on the decline. We treated 61 patients in the year 1944 as compared with 107 in the previous year. For the years 1942 and 1943 the case-fatality rate in our series was slightly over 12 per cent, whereas in the year 1944 it decreased to 6.5 per cent. This is in accord with the generally accepted opinion that the severity of the disease diminishes toward the end of an epidemic. Although we found a slightly lower death rate when sulfamerazine was used than when sulfadiazine was



administered, this may have been due to the fact that sulfamerazine was used more extensively during the later stages of the epidemic. When a small group of patients was alternated between sulfadiazine and sulfamerazine, there was no appreciable difference in the results obtained.

In a recent report<sup>9</sup> it is suggested that all patients with purulent meningitis be treated as one of the more serious varieties for the first 24 to 48 hours, pending a report from the bacteriologist giving the exact etiology. We feel that this practice is unnecessary and unwise. Among the 207 cases of meningococcic meningitis herein reported, a positive or presumptive diagnosis was made immediately from the direct examination of the spinal fluid in 188 (90.8 per cent) of the patients. Likewise, in a group of 56 patients with pneumococcic meningitis<sup>10</sup> we were able to obtain Neufeld typing directly from the spinal fluid in 42 (75 per cent). Furthermore, organisms resembling pneumococci, but in numbers insufficient for direct typing, were present even more frequently. Thus, if the centrifuged sediment of the spinal fluid is examined directly with Gram and methylene blue stains, a strongly presumptive diagnosis can be made in approximately 90 per cent of the patients with purulent meningitis.

Furthermore, an immediate examination of the spinal fluid is important because the severity of meningitis is directly proportional to the number of organisms seen in the original specimen of spinal fluid. This has been demonstrated for pneumococcic meningitis<sup>10</sup> as well as meningococcic meningitis, and in this clinic has been found to be equally true for all other purulent meningitides due to pyogenic microorganisms.

#### SUMMARY AND CONCLUSIONS

- 1 We have treated 207 patients with meningococcic meningitis during a three year period, using either sulfadiazine or sulfamerazine as the principal therapeutic agent. The gross mortality was 10.1 per cent. There was no significant difference in the case fatality rate in patients treated with the two drugs.

- 2 The number of patients treated, the case fatality rate, and the duration and severity of illness were less in 1944 than in 1943.

- 3 The etiologic diagnosis was established immediately from direct examination of the cerebrospinal fluid in 188 (90.8 per cent) of this group of 207 patients.

- 4 The factors of the greatest prognostic significance at the time of admission were the presence or absence of the coma-delirium state and the age of the patient. In patients who were delirious or in coma the finding of numerous microorganisms in or the virtual absence of dextrose from the initial specimen of cerebrospinal fluid added to the gravity of the prognosis.

- 5 There was no relationship between the concentration of the sulfonamide in the blood and the outcome in meningitis. Massive doses of these drugs are not necessary for most patients with meningococcic meningitis.

Careful appraisal of patients and of the findings in the cerebrospinal fluid will indicate those patients who require more vigorous treatment

#### BIBLIOGRAPHY

- 1 FELDMAN, H A, SWEET, L K, and DOWLING, H F Sulfadiazine therapy of purulent meningitis, including its use in twenty-four consecutive patients with meningococcic meningitis, *War Med*, 1942, **11**, 995-1007
- 2 LEPPER, M H, SWEET, L K, and DOWLING, H F The treatment of meningococcic infections with sulfadiazine and sulfamerazine (sulfamethyldiazine, monomethylsulfadiazine), *Jr Am Med Assoc*, 1943, **cxxiii**, 134-138
- 3 DINGLE, J H, THOMAS, L, and MORTON, A R Treatment of meningococcic meningitis and meningococcemia with sulfadiazine, *Jr Am Med Assoc*, 1941, **cxxvi**, 2666-2668
- 4 DANIELS, W B, SOLOMON, S, and JAQUETTE, W A, JR Meningococcic infection in soldiers, *Jr Am Med Assoc*, 1943, **cxxiii**, 1-9
- 5 OLIVER, C S, and ANDERSON, D G The treatment of meningococcic meningitis with sulfamerazine, *Am Jr Med Sci*, 1944, **ccviii**, 597-602
- 6 GOLDRING, D, MAXWELL, R, and HARTMANN, A F Diagnosis and management of severe infections in infants and children a review of experiences since the introduction of sulfonamide therapy III Meningococcal infections, *Jr Pediat*, 1945, **xxvi**, 1-31
- 7 BENEDICT, S R The determination of blood sugar, *Jr Biol Chem*, 1925, **lxxiv**, 207.
- 8 DOWLING, H F, and LEPPER, M H Toxic reactions following therapy with sulfapyridine, sulfathiazole and sulfadiazine, *Jr Am Med Assoc*, 1943, **cxxvi**, 1190-1194
- 9 DOWLING, H F, DUMOFF-STANLEY, EDITH, LEPPER, M H, and SWEET, L K. Relative toxicity of sulfamerazine and sulfadiazine, *Jr Am Med Assoc*, 1944, **cxxv**, 103-105
- 10 SWEET, L K, DUMOFF-STANLEY, EDITH, DOWLING, H F, and LEPPER, M H The treatment of pneumococcic meningitis with penicillin, *Jr Am Med Assoc*, 1945, **cxxvii**, 263-267

# COCCIDIOIDOMYCOSIS IN SOUTHERN CALIFORNIA: REPORT OF A NEW ENDEMIC AREA WITH A REVIEW OF 100 CASES \*

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WAR, and its attendant concentration of men in desert areas for training purposes, causes pulmonary coccidioidomycosis to assume increased importance. This influx of troops to sparsely settled regions carries with it an obligation for medical authorities to determine whether the infection is endemic in areas where military operations are in progress or contemplated. This seems obvious, in order that the disease may be readily recognized and proper treatment instituted from the onset, thus minimizing complications and loss of manpower.

Coccidioidomycosis may be briefly defined as an infection of the animal organism with the chlamydospores of the fungus *Coccidioides immitis*. By far the greater number of cases of the disease are of the pulmonary type, consequent to inhalation of the spores. Though infection through the skin has been adequately described, it is rare <sup>16, 27</sup>

The disease in its progressive form was first described in the Argentine in 1892, <sup>21, 31</sup> and by Rixford in 1894 <sup>22</sup> on this continent in California. The life cycle of the parasite was first described by Ophuls and Moffitt in 1900 <sup>19</sup>. The disease described by these early workers was termed coccidioidal granuloma and was known then, as now, for its somewhat macabre prognosis. In 1937, on the contrary, some 40 odd years after the original description, it was shown by Dickson and Gifford <sup>6, 7, 12</sup> that most cases of the disease are benign with a very good prognosis. The work of Dickson established beyond doubt the etiological relationship between *Coccidioides immitis* and "Valley Fever," and moreover, fulfilled the prediction made by K. F. Meyer <sup>1\*</sup> on purely theoretical grounds that a benign form of the disease should exist and would be found eventually. For further information concerning the development of this phase of the subject the reader is referred to those excellent articles of the original workers <sup>6, 7, 11, 12, 18, 19, 23</sup>.

The causative organism manifests two phases of reproduction. The so-called saprophytic phase, seen in cultures and presumably in nature, is considered to end in the production of spores called chlamydospores. Possibly these are formed under adverse conditions, as is the case of other spore formers. Certainly, large numbers of these chlamydospores appear in old cultures as the media dries out. Of its propagation in nature, very little is known. Soil cultures have been made successfully <sup>5, 9, 30</sup> but with some difficulty <sup>20</sup>. Smith and his co-workers <sup>27</sup> have examined the roots of vegetation

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from various soil levels in an attempt to obtain more evidence of the natural phases with no success. The soil of infected areas is almost always of an alkaline, calcareous type.

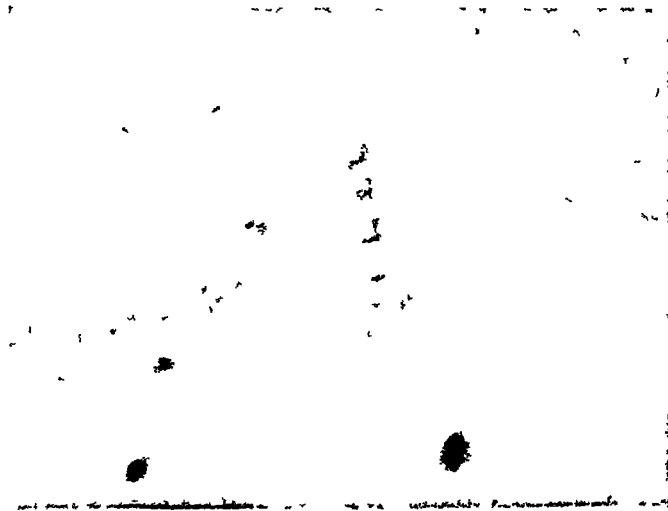
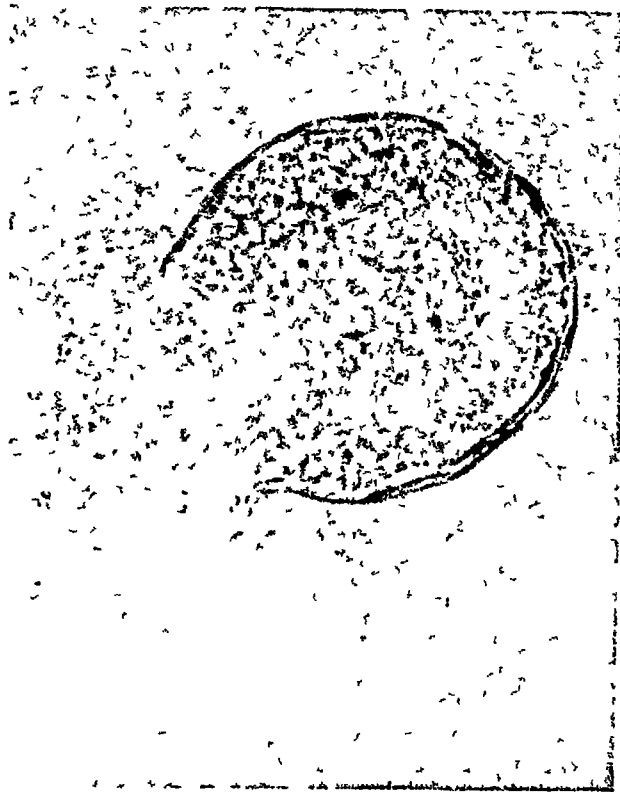


FIG 1. (*Abaze*) Endospores rupturing from spherule.  
FIG 2. (*Belou*) Dice-like chlamydospores.

The parasitic phase of the fungus is seen only in animal tissues and sputum or exudate,<sup>17</sup> and characteristically appears as a doubly refractile spherule containing endospores. Eventually these endospores burst from the parent spherule and in turn become spherules containing endospores.

The presence of these spherules in cultures of special strains of the organism has been reported by Baker and Mrak<sup>1</sup>

Emmons<sup>8, 9, 10</sup> has demonstrated that a certain number of small rodents trapped in the Southwest were infected with *Coccidioides immitis* and also with *Haplosporangium parvum*<sup>10</sup> Between these two fungi Emmons has shown some relationship, both by cross sensitivity to skin tests and the presence of microscopic lung lesions caused by *Haplosporangium parvum* in wild rodents and experimentally infected white mice He feels that coccidioidomycosis is primarily a rodent disease transmitted to man only accidentally through the medium of dust contaminated with the spores by rodents He also invokes the factors of host (perognathus, dipodomys) and climate to explain the lack of spread from the areas in which the disease is known to be present although these points are debatable He suggests that in areas to be made the site of troop movements or other widespread activity, samples of the rodent population should first be examined for fungus infections

Despite the fact that California has long been known to harbor the fungus in the San Joaquin Valley and other limited areas, it seems desirable to report a new and rather large endemic area as a guide to further studies in this region Specifically, we should like to report that region, roughly triangular, bounded by Banning and Needles, California, and Yuma, Arizona, as a new endemic area for *Coccidioides immitis* This desert region is spottily infected with the fungus of *Coccidioides immitis* and proof of this statement may be adduced from the following description of our studies in the area

#### EPIDEMIOLOGY

From time to time, an occasional case of coccidioidomycosis had been seen on the Medical Wards of the March Field Station Hospital Invariably these patients had acquired their infections in the San Joaquin Valley Being suspicious of the desert and surrounding regions of the Southern California area,<sup>16, 27</sup> we began making routine skin tests using coccidioidin antigen on all patients with chest disease regardless of the suspected etiology This applied particularly to the numerous cases of so-called primary atypical pneumonia being seen at that time A careful travel history was taken on all positive reactors and special attention was paid to the itinerary and activities of the individual for the two months prior to hospital admission, with emphasis on assignment and activities in endemic or suspected areas Obviously, a positive skin test in an individual who had always lived in a non-endemic area before coming to California was of greater significance than a positive reaction in a person from some known endemic region

In April 1943, 12 colored soldiers were admitted to the hospital with acute pulmonary coccidioidomycosis These soldiers were all from the same organization, engaged in a recently begun construction project near Banning, California

Quite naturally, the possibility of proving a new endemic region suggested itself. The main effort consisted of repeated skin tests on 573 soldiers representing both colored and white troops, performing a dusty type of work at the edge of the desert. These intradermal skin tests were performed at periodic intervals between April 1, 1943, and July 26, 1943, using coccidioidin antigen in a dilution of 1:1,000. The antigen was furnished by Dr. C. E. Smith of Stanford University Medical School as part of the work of the Commission on Epidemiological Survey of the Board for the Investigation of Epidemic Diseases in the Army. One hundred and 35 "change overs" from negative to positive skin reactions were found, of which 83 were hospitalized with acute pulmonary coccidioidomycosis. The remaining 52 had insufficient findings to warrant hospitalization, however, these men were carefully followed and finally classified in the clinically inapparent group since no symptoms or objective findings ever appeared. The 135 cases which showed a change in the skin reaction from negative to positive (change overs) constitute the original epidemiological group by which the area of endemicity was established.

TABLE I  
Troops in Survey Area

|         | Number | Percentage |
|---------|--------|------------|
| White   | 214    | 37.3       |
| Colored | 359    | 62.7       |
| Total   | 573    | 100        |

TABLE II  
Reactors in Original Epidemiological Group

|                                  | White  |          | Colored |          | Total  |          |
|----------------------------------|--------|----------|---------|----------|--------|----------|
|                                  | Number | Per Cent | Number  | Per Cent | Number | Per Cent |
| Positive Skin Tests              | 47     | 22       | 88      | 24.5     | 135    | 23.6     |
| Hospitalized Cases (From Survey) | 34     | 15.9     | 49      | 13.6     | 83     | 11.1     |

It is of interest to consider the incidence of infection in the two racial groups working in the desert under similar conditions. There were 214 white troops of whom 47, or 22 per cent, acquired positive skin tests in the area, of whom 34, or 15.9 per cent, were hospitalized. Of 359 colored troops 88, or 24.5 per cent, acquired positive skin tests, and 49, or 13.6 per cent, were hospitalized. In summary, 573 men were exposed, and 135, or 23.6 per cent, acquired positive skin tests, of whom 83, or 14.4 per cent, were hospitalized for acute pulmonary coccidioidomycosis.

Because of the above, the Surgeon General was notified on June 1, 1943, that according to the findings, a considerable part of the desert area was probably endemic for coccidioidomycosis.

In the eight months subsequent to the epidemiologic survey, 17 additional patients with acute pulmonary coccidioidomycosis have been hospitalized from the desert area, thus making a total of 100 hospitalized cases, almost equally divided between colored and white patients. In addition, during the year which has elapsed since the survey, one of us (FMW) has seen many patients with this disease in various hospitals throughout the desert and in those hospitals which serve as evacuation points for the desert. Moreover, civilian cases of coccidioidomycosis have been reported in this general area also with typical findings, including erythema nodosum and positive skin tests. Some of these civilian patients have been seen by us in consultation. These additional facts are offered as further proof to substantiate the epidemiological findings of the presence of the fungus.

Since all of the soldiers tested had been at March Field within three months prior to transfer to the desert, it was considered necessary to prove that the infection was not acquired at the Field. A control group was selected whose activities were confined to March Field or its immediate environs. Skin tests repeatedly performed on this group of 182 individuals over a six month period were consistently negative.

### DIAGNOSIS

The cases reported here presented no diagnostic problems. Eighty-three of them were hospitalized with a diagnosis as a result of the epidemiological survey, and 17 additional cases were hospitalized from the desert area. This is an unusual circumstance, quite different from the average situation confronting the Medical Officer in single cases. Of importance is a high degree of suspicion concerning this disease, if one is to make the diagnosis in individual cases.

The history is paramount, with reference to the residence, assignment, travel or recent activity in a known or possibly suspected area. The commonly accepted incubation time is from eight to 21 days, though the average is around two weeks<sup>5, 11, 23, 24, 25</sup>. Those accustomed to dealing with this disease are suspicious of its presence in any arid type of terrain, where long dry seasons and milder winters prevail. In general, the known endemic areas on this continent are portions of California, Arizona, New Mexico, Mexico and West Texas<sup>20</sup>. It is known to occur in Argentina and may well exist in other arid areas of the world. Rarely, cases of infection have resulted from merely passing through endemic regions by conventional transport<sup>23, 24</sup>. As might be expected, exposure and activity for somewhat longer periods of time usually result in a proportionately greater number of acute infections, especially in newcomers with occupations involving dust or work near the soil<sup>23</sup>. The occasional case occurring in individuals who have never been in an area even slightly infected is probably best explained by the accidental inclusion of a few chlamydospores along with some agricultural or other product derived from an endemic region.

Briefly, in any case with a pulmonary ailment and a history of recent travel in known or suspected areas, coccidioidomycosis should be considered in the differential diagnosis

### SYMPTOMATOLOGY

Most authorities agree that by far the greater number of initial infections with coccidioidomycosis are of the inapparent or asymptomatic type. This is made evident by the intensive and illuminating work of Smith<sup>23</sup> in the San Joaquin Valley where large numbers of persons have positive skin tests and yet have never experienced an illness or symptoms which might be attributed to infection with *Coccidioides immitis*.

These cases reported here were also interesting in that many of the individuals comprising the series were hospitalized early, before the onset of symptoms of any magnitude. A few remained free of symptoms throughout the duration of the hospital stay, despite roentgenologic and serologic evidence of infection. However, symptoms elicited before and during hospitalization were essentially the same as those reported many times by others and were as follows:

**Fever.** Eighty cases, 80 per cent, had fever of some degree on admission, or after hospitalization, but the height and duration varied greatly. The temperature was usually remittent in character, and lasted in individual cases from one to 52 continuous days. The average duration of initial fever in white patients was four days, and in colored patients it was eight days. The absence of fever did not necessarily prove to be a good prognostic sign since many of the more severe cases remained afebrile throughout the greater part of their hospital stay, and occasionally, new evidence of activity would not be accompanied by a concomitant rise in temperature. As a concrete example of this, one patient developed the progressive form without any rise in temperature whatever.

**Chest Pain.** This symptom was present in 73 cases, 73 per cent of the series, and occurred in varying degree and location. Usually it was described as a feeling of tightness or constriction, more pronounced on the involved side, and aggravated by deep breathing or coughing. Ordinarily chest pain was not present after the acute stage, however, some few cases showed a persistence of the symptom, especially on exertion, for a period of months despite essentially negative physical, roentgenologic, and serologic examinations. Several cases showed definite localization of pain. One case in particular was suspected of having a fractured rib as a result of slight trauma to the chest a few hours prior to hospital entry. There was no fractured rib, but there was a pronounced pleural friction rub present.

**Cough.** This symptom was present in 64 cases, 64 per cent, and was, with rare exception, non-productive. In three cases, 3 per cent, the cough produced transitory blood-streaked sputum. The absence of sputum in most of the cases largely curtailed the use of sputum examinations as a means of diagnosis.



*Joint Manifestations* Joint symptoms developed in eight cases, 8 per cent, at approximately four to 14 day intervals after hospital entry. Six cases, 6 per cent, were in conjunction with skin lesions and three of these cases had mild phlyctenular conjunctivitis.

The arthritis was characterized by moderate heat, very slight swelling, and much subjective complaint upon the smallest movements of the joint involved. Characteristically, several joints were involved, principally knees, ankles, and elbows, though no migration was observed. This symptom rarely persisted more than 10 to 12 days.

*Cutaneous Manifestations* Erythema nodosum is one of the striking symptoms associated with infection by *Coccidioides immitis*. It has been used as a theoretical index by epidemiologists to compute the approximate number of cases occurring in a given region by using a percentage factor. Smith believes this cutaneous manifestation occurs in about 2 per cent to 5 per cent of infections<sup>5, 25, 29</sup>. In 135 infections of the original epidemiological group there were six cases or 4.4 per cent. All six cases had lesions over the tibial areas of both legs, characterized by reddish purple, tender, raised nodules in the skin, which recovered spontaneously leaving small areas of pigmentation for several weeks or months. All cases of erythema nodosum occurred in conjunction with joint symptoms. Two of the cases presenting joint symptoms and erythema nodosum were in colored patients. This was of sufficient rarity to demand further investigation, and upon questioning, it was found that both men had mixed ancestry.

*Erythema multiforme* was another cutaneous response seen in two cases, 2 per cent. This was confined to the face, neck, shoulders, arms, hands, and upper trunk, and occurred only in white patients. Neither case had any other skin lesion, nor did they have joint symptoms. The skin cleared in approximately seven to 10 days.

*Urticaria* was seen in two white cases, 2 per cent, and was of a generalized type, noteworthy because of severe pruritus, and our inability to allay the discomfort by whatever means attempted.

TABLE III  
Incidence of Skin Manifestations

|  | Erythema nodosum |          | Erythema multiforme |          | E nodosum and E multiforme |          | Urticaria |          | Total Skin Manifestations |          |
|--|------------------|----------|---------------------|----------|----------------------------|----------|-----------|----------|---------------------------|----------|
|  | No               | Per Cent | No                  | Per Cent | No                         | Per Cent | No        | Per Cent | No                        | Per Cent |
| In the 135 cases composing the original epidemiological group  | 6                | 4.4      | 2                   | 1.5      | 8                          | 5.9      | 2         | 1.5      | 10                        | 7.4      |
| In the 152 cases composed of the original 135 plus the 17 additional cases hospitalized in the next 8 months | 6                | 4        | 2                   | 1.3      | 8                          | 5.3      | 2         | 1.3      | 10                        | 6.6      |

*Malaise* As a diagnostic feature too much emphasis should not be placed on this symptom. It was elicited in questioning, and in general covers the all embracing term often used by a colored soldier, "Ah jus' feels bad all over." Such a condition was present in 43 cases, 43 per cent. It was found in the early stages only, and did not persist longer than three or four days, though there were some exceptions to this general statement.

*Anorexia* This was definite in 30 cases, 30 per cent, and persisted up to 10 days in a few patients, though as a rule appetite returned in full after four or five days. As a diagnostic symptom it was not helpful.

*Headache* This symptom occurred in 27 cases, 27 per cent, and was definite. It was of a generalized nature in all cases. Several patients had headache of such severity that it was considered necessary to do spinal puncture, though no definite neurological symptoms were present. The spinal fluid was normal in all cases where puncture was done. The majority of cases with headache ceased to have this symptom after one week. There were, however, two cases in which the complaint persisted in severe degree for over a month, despite a complete neurological, otorhinolaryngological and roentgenographic study. The reason for this is not evident. Both cases were in colored soldiers.

*Pharyngitis* This symptom was present in 20 cases, 20 per cent, with both the subjective complaints attendant thereto, and the objective findings of an injected moderately inflamed pharynx. This finding cleared rapidly in a few days after hospital entry, in no instance lasting longer than seven days. No exudate was described in any case. In 12 per cent barely palpable cervical glands were present. Smears and cultures of the throat were negative for significant organisms.

*Chills*. This symptom was present in 12 cases, 12 per cent, as a definite shaking chill. Not included were those whose description or findings were merely "chilly" sensations. Several patients with chills were actually observed on the wards and there can be no doubt about the quality of the chill. Numerous other patients related having "chilly" sensations.

*Conjunctivitis* was seen in only four cases, 4 per cent, and is only mentioned to complete the record. The cases so included were definite and occurred in connection with other manifestations described above.

*Hemoptysis* was seen in three cases, and was never more than mild blood streaking of the sputa. This symptom was only transient and was not particularly helpful diagnostically. It also is included for the record.

In conclusion, except for the persistence in a few cases of certain individual symptoms, as noted, the average case became asymptomatic, and usually experienced a rather pronounced feeling of well being in less than ten days.

#### PHYSICAL EXAMINATION

The physical examination in most instances is only moderately helpful as a definitive procedure. As may be judged, most of these patients are

obviously suffering from a respiratory infection and may have signs of fever, cough, and mild to moderate prostration at the onset. The pharynx may show a diffuse injection, but exudate was not seen in any of these cases. Examination of the chest may show signs of consolidation or fluid. Again, there may be a well localized pleural friction rub. Less than these easily identified physical signs, there may be a few râles, slight suppression of breath sounds or no perceptible variation from normal. Otherwise, unless there are skin or joint manifestations, the physical examination is usually not revealing. In the case of progressive or disseminated coccidioido-

### FREQUENCY OF SYMPTOMS IN 100 CASES HOSPITALIZED FOR PULMONARY COCCIDIOIDOMYCOSIS

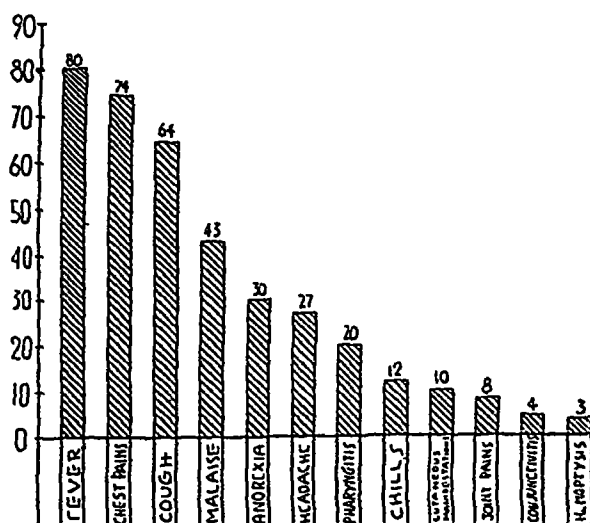


TABLE IV

mycosis, the skin or subcutaneous tissues may show nodules or small abscesses, again, there may be signs of meningitis, though we did not see this in any case.

### ROENTGENOLOGICAL EXAMINATION

The roentgenogram was of great help both in diagnosis and in following the course of the disease. It is not the purpose of this paper to discuss the roentgenologic findings. For that the reader is referred to such excellent articles as those of Carter, Winn, and Colburn<sup>2, 3, 4, 22, 23</sup>. The roentgenologic findings for practical purposes may be roughly divided into the following categories:

- 1 Varying degrees of parenchymal infiltration, ranging from the most minimal lesion to that of consolidation.

2 Hilar adenopathy and thickening, not infrequently seen in connection with the parenchymal lesion

3 Fluid, in varying amounts

4. Nummular densities—single or multiple—usually in our experience indicative of old and focalized coccidioidomycosis

5 Cavitation. This feature in all cases occurred as a late complication of the acute phase The typically thin-walled cavity so often described was

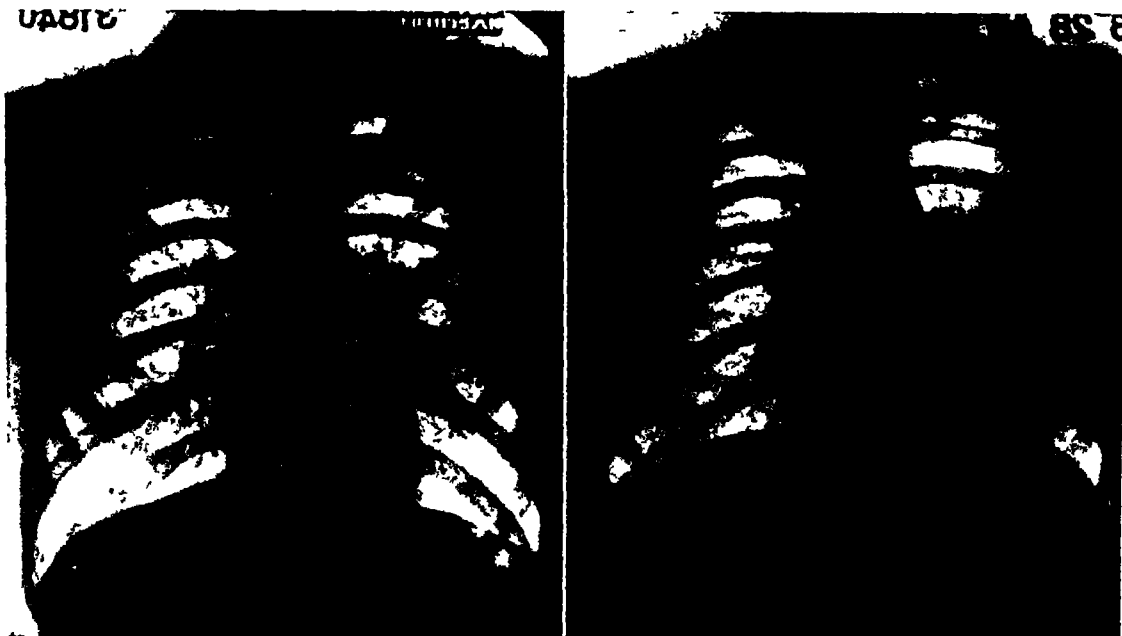


FIG 3 (Left) Bilateral hilar adenopathy

FIG 4 (Right) Marked parenchymal infiltration in the left lung field



FIG 5 (Left) Left apical parenchymal infiltration similar to that seen in tuberculosis

FIG 6 (Right) Fluid filling the right pleural cavity



FIG 7 Cavity formation in fifth right interspace

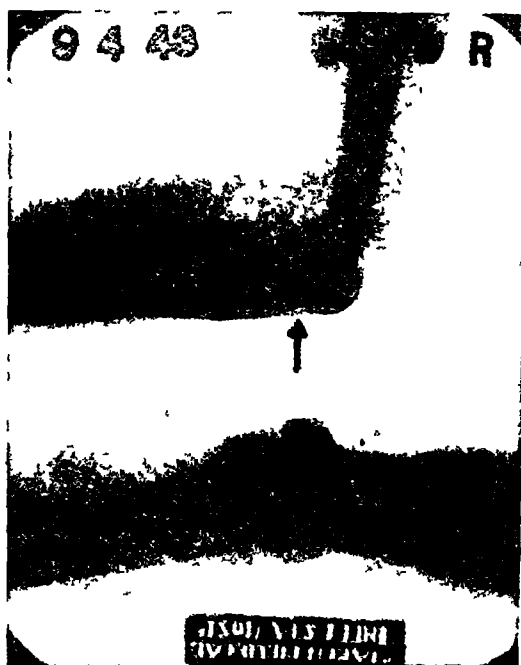


FIG 8 Bone defect in ulna resulting from dissemination

not seen as such at first. In serial films, cavitation occurred in a region which was the final area of consolidation, usually rather dense and well circumscribed. In the center of this area a rarefaction would appear, thus giving rise to a cavity surrounded by a relatively wide zone of residual reaction. Gradually, there was some narrowing of this peripheral zone so

that eventually a relatively thin-walled cavity remained. Usually these are found below the clavicle, and such was the case in all those cavities seen by us.

6 Bone lesions in roentgenograms showed well circumscribed areas of bone destruction, with some tendency to bone proliferation and elevation of periosteum. It so happened that the two bone lesions seen by us were in the proximity of joints at the end of long bones, though joint spaces were not invaded. It was impossible for us to follow the course of this type of lesion because these patients were transferred to Veterans Facility for long term care. However, with one exception, subsequent information received from the Facilities is of an optimistic tone.

### SKIN TEST

This is probably the most helpful single test when used in conjunction with other aids, i.e., travel history, roentgenogram, sedimentation rate, differential blood count, and serological studies. The time required for the development of a positive skin test, according to most authorities, ranges from two days to four weeks. One case in this series required six weeks, which is unusual in the experience of most workers<sup>23, 25, 26</sup>. A recent previous negative skin test, followed in time by a positive one, is evidence of almost unquestionable validity in making the diagnosis. Kessel has shown that there is no cross sensitivity to tuberculin<sup>15</sup>. However, as mentioned previously, Emmons raises the doubt of cross sensitivity with *Haplosporangium parvum*<sup>10</sup>.

The generally advocated strength of antigen for routine testing is a dilution of 1:100<sup>25, 27</sup>. This is best if one has time only for one test and is willing to overlook the occasional large area of swelling and edema seen when using this strength. However, where coccidioidomycosis was suspected, and especially in hospitalized patients, we felt it was better to begin with a 1:1,000 dilution, and failing there, to use the 1:100. The optimal time for reading the skin test is 36 hours, but in the field, reading them at 48 hours was a more practical compromise. In the hospital skin tests are read at 24 and 48 hours, just as the intradermal tuberculin test. It is also very important to use new tuberculin syringes never before used for any other antigen in doing the skin test for *Coccidioides*. This avoids false positives by contamination with other antigens<sup>27</sup>.

A word of caution should be added concerning negative skin tests in persons with an illness showing features consistent with the diagnosis of coccidioidomycosis. Progressive or disseminated cases of the disease may have complete loss of sensitivity to coccidioidin antigen of any strength. It is here that sputum examinations, serological studies and biopsy are of value.

In summary then, failure to react to coccidioidin used as an intradermal skin test in a concentration of 1:100, rules out the possibility of coccidioidomycosis, except in those patients with disseminated infections, provided a sufficient time has elapsed to permit the individual to develop the sensitivity necessary to produce the reaction.

## BLOOD AND SEROLOGICAL STUDIES

These were represented by the differential total white blood cell count, erythrocyte sedimentation rate (Wintrobe), and serological studies with complement fixation and precipitin tests. The serological studies were done for us by the Commission on Epidemiological Survey in its study of coccidioidomycosis at the Stanford University School of Medicine.

The differential and total leukocyte count was of interest mainly because of the eosinophilia which appeared in these cases, and has been seen by others<sup>7, 27</sup>. On admission most patients showed some increase in eosinophiles, varying between 5 per cent and 18 per cent of the total leukocyte count. This ranged upward in subsequent counts during the second and third weeks of illness. In one patient, the eosinophile count rose to 30 per cent. There was a decline in the eosinophile count to normal levels in most cases after a maximum of four weeks, though in a few, moderate eosinophilia persisted up to six weeks. All cases of eosinophilia had at least one stool examination for parasites and ova, none being found. Briefly, polymorphonuclear increase of mild degree was seen in 35 cases, 35 per cent, ranging from 10,000 to 15,000. Sixty-four cases, 64 per cent, showed a white blood cell count under 10,000. One patient had a leukocytosis of over 20,000, and was at first considered to have lobar pneumonia because of the antecedent chills, fever, signs of consolidation confirmed by roentgenogram, and the white blood cell count. He was given sulfadiazine without effect, until the positive skin test became apparent in the ensuing 36 hour period.

The erythrocyte sedimentation rate was of considerable value. This was increased in all patients on admission and varied between 16 mm/hr and 46 mm/hr. All expressions of this test reported here are corrected, using the Wintrobe method. The test was useful in both the diagnosis and the prognosis. Our practice was to have a normal sedimentation rate, along with other arbitrary standards, for at least 14 days before ambulatory privileges were given. Sedimentation rates were done at weekly intervals.

The serological studies were of inestimable value both in making a definite diagnosis and in following the course of the disease. There were a few cases which showed entirely negative precipitin and complement fixation tests, even though we had previously found a negative skin test, followed later by a positive one (change over), with roentgenologic signs of mild parenchymal infiltration, slight eosinophilia, and a sedimentation rate in the twenties. These were usually reported to us as having such a mild infection that it was insufficient to stimulate humoral antibodies. On the other hand, most of our cases showed definite serological reactions, with moderately high initial titer of precipitins, followed in turn by a variable though consequential titer by complement fixation.

It was of interest to us that Dr. Smith was able to predict in most instances, that certain patients were not doing well, or the converse, solely by serological tests. Dissemination was predicted before it occurred in every

case by the serological tests on the basis of high titers in complement fixation. This was regardless of the reaction to the skin test, which in one instance of dissemination, as previously mentioned, was completely negative. Needless to say, with such a record, we used the declining antibody titer as another index of safety in mobilization of the patient.

We have, in general, come to place a great deal of reliance in this relatively clear-cut test and only hope its early availability to all laboratories will bring it to the fore as a needed aid to diagnosis and prognosis for those treating this disease.

### SPUTUM EXAMINATION

This examination consists of two phases.

1. Direct examination of a small amount of sputum mixed with 10 per cent sodium hydroxide on a slide with cover glass, after waiting a short time for clearing of the preparation. By this method, we were able to demonstrate a doubly contoured spherule containing endospores in 28 cases, 28 per cent. This examination requires experience and extreme care in interpretation.

2. Cultures of all sputa were made and were positive in 61 cases, 61 per cent. All cultures were not verified by animal inoculation, as a practical concession to our particular situation. Most cultures were kept until they were older and were then examined for chlamydospores, a particularly dangerous procedure and certainly not to be recommended. It is either a fortunate circumstance, or the result of unusual technic, that only one member of the laboratory staff became infected, developing a mildly positive skin test but no clinical signs of the disease. Such practice was discontinued instantly upon discovery.

All sputa were examined a minimum of six times by both direct and culture methods for tubercle bacilli and none was found in the entire series by either method.

In general, our impression of the sputum examination in the diagnosis of coccidioidomycosis is that it is not an entirely satisfactory method. Certainly it is helpful, but the failure to find or cultivate the organism does not exclude the diagnosis, and the culture method is slow, dangerous, and to be absolutely certain, requires animal inoculation as a final measure. Our best results with sputum examinations were obtained by using sputum coughed up in the early morning, after the patient had rinsed the oral cavity with 50 per cent alcohol solution.

In summary, the following factors are important in the diagnosis.

1. History of recent exposure to dust in a known or suspected endemic area.
2. Symptoms and physical findings as outlined above.
3. Positive skin test.
4. Elevated sedimentation rate.



- 5 Roentgenologic findings in the chest
- 6 Serological findings
- 7 Eosinophilia (need not be present)
- 8 Sputum examination, direct and culture

In the final analysis, a presumptive diagnosis could be made in those patients who came from a known or suspected endemic area with signs of a respiratory infection and a positive skin test. If in addition, there was roentgenologic evidence of lung or hilar involvement, the diagnosis was probable. Definite diagnosis could be made in cases showing the above with positive serological studies, biopsy or animal inoculation with recovery of the organism. A recent change-over in the skin test from negative to positive would fall in the last category.

### COMPLICATIONS

Cavitation and dissemination are the two main complications in our experience. The latter is of far greater importance than the former although probably less frequent.

*Cavitation* Cavitation of the lung occurred in six cases, 6 per cent, four of which were in colored, and two in white soldiers. Smith<sup>25, 26, 27</sup> considers cavitation no menace to the patient, either present, or future, the lesion being a "focalization" of the disease which excavates more or less mechanically. Such patients are generally considered resistant not only to exogenous, but to endogenous infection as well. The cavity, if old, is usually a thin-walled anatomical defect in the lung parenchyma, or if recent may be surrounded by a zone of increased density, presumably representing residual reaction in the area from which it formed. Such a cavity, the result of coccidioidal infection, is almost always a "silent" one. Rarely hemoptysis is seen, or if complicated by secondary infection or tension effects, symptoms may arise. Conservative treatment such as absolute bed rest, sandbagging the affected side of the chest, or tight strapping, will in a goodly percentage of cases be rewarded by closure.<sup>27</sup> Pneumothorax is successful in a certain number.<sup>27</sup> Surgical measures such as lobectomy, seem inadvisable in most instances, though there may be exceptional circumstances where such could be applied with benefit.<sup>20, 27</sup> It seems wiser, however, to exhaust less radical measures before operation is attempted, especially when dealing with so-called "silent" cavities. Also of some importance, and in contradistinction to cavities of tuberculous origin, those patients with coccidioidomycosis cavities are not a menace, either to themselves or their associates in that they are non-infectious.<sup>20</sup> Spontaneous closure may be seen. A brief discussion of end results so far as observed in our cases seems worthwhile.

Two cases of cavitation in white soldiers showed favorable end results. One case (number 1) in which the original cavity measured 1.75 centimeters in diameter, cleared entirely leaving a small residual fibrosis in the lung parenchyma. This case required 144 days, 102 of which were hospital days.

and 42 of which were on out-patient status, before closure of the cavity was effected. After the acute phase of the disease, he was free of symptoms for the entire time. Subsequent observations for three months showed him to be well and in good health, with the chest roentgenogram reported essentially negative. The second patient, whose outlook is equally optimistic, had a one centimeter cavity in the right lower lung parenchyma, which was presently closing, but had not completely done so after 61 days of hospitalization. He was asymptomatic and was on a bed rest regimen, aided by strapping and sand bags to the right lower chest, for whatever benefit may accrue from this measure.

Four cases of cavitation occurred in colored soldiers. In general, the results achieved by hospitalization were less favorable than with the white group, although identical hospitalization and attention were given to both. The following are colored cases.

Three cases of cavitation were transferred to Veterans' Facility for further hospitalization. This was considered necessary because of lack of satisfactory general progress as evidenced by fever at intervals, fast sedimentation rates, and serological titers of a high dilution, as well as the persistence of cavity by chest roentgenograms, with no tendency to close. One of these cases disseminated to bone, which was added reason for the transfer. These three cases had four months of military hospitalization under optimal conditions.

The fourth case was of considerable interest. This colored male after hospitalization for acute pulmonary coccidioidomycosis, ran the usual course, with findings clinically and roentgenologically of a severe case. Serological studies showed confirmatory high titers. Sedimentation rates were elevated, and sputa were positive for *Coccidioides immitis*, and negative for *Mycobacterium tuberculosis* on several direct examinations.

After 30 days of hospitalization a cavity, one centimeter in diameter, developed in the right second interspace anteriorly on chest roentgenograms. He was returned to light duty after 90 days of hospitalization, inasmuch as his condition fulfilled the standards that had been set for return to duty, namely, clinical well being, normal sedimentation rate, static or declining serologic reactions, and a roentgenogram which showed a static lesion, in this instance the small cavity. All studies for tuberculosis were negative, including gastric lavage with guinea pig inoculation.

Ten weeks later, after being observed at intervals in the out-patient department, he was readmitted to the hospital because of fluid in the right pleural cavity. Physical examination was essentially negative save for signs of fluid in the right chest. Chest roentgenogram confirmed this, and the persistence of the cavity in the right upper lobe. The sedimentation rate was 24 mm/hr (Wintrobe corrected). During the early part of this hospitalization there was an occasional rise of temperature to 99° F, but this was normal otherwise.

Thoracentesis was performed with aspiration of 650 cc of straw-colored fluid, containing 100 per cent lymphocytes. The specific gravity was 1.029. Direct examination of the fluid was negative for bacteria or fungi. A guinea pig inoculated with the fluid showed no evidence of tuberculosis or coccidioidomycosis. Serological study showed a slight decline in titer from the previous hospital entry, indicating that the infection was being well handled. A tuberculin skin test (purified protein de-

rivative) first strength was negative, but the second strength showed a two plus positive. No sputum was produced at any time, though gastric lavage samples again inoculated into a second guinea pig were reported negative for both tuberculosis and coccidioidomycosis.

The further course of this case was uneventful, being characterized by absorption of the pleural fluid and closing of the cavity. The chest roentgenogram reported only a moderate blunting of the right costophrenic angle, with slight residual fibrosis in the area of the cavity. The sedimentation rate was normal (8 mm) after the first month of bed rest. He was returned to duty after 60 hospital days, free of symptoms and apparently well. Subsequent observation for three months found this patient well and in good health with no essential abnormalities in the chest roentgenograms, or other laboratory data, except for the persistence of a moderately high serological titer, and even this was on the wane.

It can rightly be argued that the pleural effusion was possibly, or even probably, on a tuberculous basis and not coccidioidomycosis at all. It is our feeling, however, that the fluid was on the basis of coccidioidomycosis. He is being observed at monthly intervals for any change of status.

In summary then, two cases of cavities in white soldiers either closed or showed strong tendency to close at the last examination. Of four cases of cavitation in negroes, only one closed and that after a rather unusual course involving pleural effusion. The three remaining cases of cavitation in colored men have been transferred to Veterans' Facility for long term treatment, one case being of a disseminated type. Three of the six cases of cavitation, regardless of racial incidence, will undoubtedly be on full military duty in a short time, whereas the three remaining cases were lost to the military service. The question might be raised as to why we did not use pneumothorax. This is a form of long term therapy which was considered inadvisable in a station hospital. It is the opinion of this staff that the end results would not have been markedly different in the event this procedure had been instituted. That, however, is debatable.

#### DISSEMINATED OR PROGRESSIVE COCCIDIOIDOMYCOSIS

The disseminated form is by far the most serious type of infection by *Coccidioides immitis*. In this form, the prognosis is considered poor, with usually less than an even chance of recovery. The chances of dissemination, statistically,<sup>25</sup> seem rather small, since large surveys made by Smith<sup>11, 24</sup> show a rate of dissemination of about one in 500 cases. Small as this figure might seem, it none the less urges caution and conservatism in the treatment of uncomplicated cases of acute pulmonary coccidioidomycosis. Any attitude less than this may well reduce the favorable prognosis associated with the uncomplicated form.

Despite the conservative treatment accorded the patients in this series, the disseminated form occurred in four cases, 4 per cent, all of which were in colored soldiers at complete bed rest. Of the 49 colored patients represented in this series, this represented a 12 per cent rate of dissemination, a figure almost unbelievably high. Moreover, it confirms strongly what has long been known, namely, that the dark skinned races handle this disease poorly.<sup>27</sup>

It would seem worthwhile in the light of this to consider carefully the areas into which colored troops are being sent, particularly if the area is known or suspected as an endemic one for this fungus. A brief discussion of the four disseminated cases follows, though no extensive data are presented.

Of the four cases, one ended fatally (see below), with a generalized military dissemination, involving virtually every organ and system of the body except the gastrointestinal tract and central nervous system. Of the other three, two cases had dissemination to bone, and the last disseminated to muscle. The latter case was proved by biopsy of the muscle tissues, revealing typical spherules of *Coccidioides immitis*. In those patients showing bone involvement no attempt was made to biopsy the bone lesions, for in the presence of clinical, serological, and roentgenologic findings there seemed no doubt of the validity of the diagnosis.\*

#### TREATMENT AND CRITERIA FOR RETURN TO DUTY

**Treatment** The average case of acute pulmonary coccidioidomycosis has an extremely good prognosis for complete recovery. Barring dissemination or complicating cavitation, the average case is almost in the class of a self-limited disease, given proper treatment. There is no "specific" for the disease.<sup>27</sup> Simple measures such as aspirin, codeine in small doses, or other mild analgetics are usually quite sufficient to handle the acute symptoms of the disease. Vaccines have been used with questionable results. Roentgen-ray has been suggested, though no large series has been reported using this agent. Immunotransfusions from patients with high titers of antibody have been used by us and others,<sup>14</sup> with no convincing results. Surgical excision has been used on local abscesses caused by the fungus, and reported favorably,<sup>11</sup> though further exploration of this measure is in order.

The main essential of treatment is adequate bed rest, and until the patient is markedly improved this should be absolute bed rest.<sup>27</sup> Once the patient has been mobilized, his eventual disposition is a problem facing all medical officers attending such cases. The following standards for return to duty were established and used at this hospital on all cases reported here.

**Criteria for Return to Duty** (1) The patient must be clinically well, with freedom from symptoms and fever for at least three weeks, and preferably one month.

(2) The chest roentgenogram should show a relatively clear picture, or at least minimal findings with no evidence of activity for one month. The term activity is used to denote either improvement or extension of the chest lesion. Practically, one could not hope to keep some of these cases until the chest was reported clear, for many carry residual nummular densities or slight fibrotic reactions for months or even years. If the chest roentgenogram showed the lesion to be static and minimal, and the patient had reached

\* Since this is being written, correspondence from the Veterans' Administration reveals that one of the cases of bone dissemination was disseminated to other body structures so that he now has three distinct areas involved.

what seem like maximal benefit from hospitalization, the other laboratory factors noted below being in keeping, we felt safe in returning that man to light duty for periodic observation at monthly intervals. In no instance did this produce any seriously adverse results.

(3) The sedimentation rate should be within normal limits on at least two weekly intervals and preferably for three weeks or one month.

(4) There should be no evidence of increased activity as shown by serological studies. Although it was desirable to see a decline in the serological reaction, practically it was necessary to be content in some cases with a static or slightly declining titer.

(5) There should be no evidence of dissemination.

Despite these precautions, one colored patient developed evidence of a disseminated lesion to bone one week before he was scheduled to return to duty. He was retained in the hospital and transferred to Veterans' Facility for further care. No dissemination occurred in any patient who was returned to full duty, and it is our impression that rigid adherence to the criteria as outlined most certainly helped in avoiding dissemination.

#### PRESENTATION OF ILLUSTRATIVE CASES

The following cases have been chosen because they illustrate different aspects of pulmonary coccidioidomycosis. The first is that of an average case with complete recovery, the second is one in which pleural effusion occurred, and the third is a case of dissemination to muscle. The last patient illustrates a case of progressive coccidioidomycosis which ended fatally.

The following is an illustrative average case.

The patient was a well developed, well nourished, 36 year old white male who entered the hospital on May 16, 1943 because of hoarseness, chest pain, and non-productive cough of two weeks' duration. He had been in the desert area for about one week before the onset of these symptoms. His temperature on admission was normal but physical examination revealed an urticarial rash over the legs and thighs. The pharynx was mildly injected and breath sounds were increased at the left base. His white blood cell count on admission was 11,400 with 72 per cent polymorphonuclears and 5 per cent eosinophiles. Roentgenogram of the chest revealed parenchymal infiltration extending from the left fourth rib anteriorly to the diaphragm and from the heart border to the chest wall.

The day following admission into the hospital the patient began to have fever which continued for the next 13 days. A coccidioidin skin test 1:1,000 dilution was positive and blood was sent to Stanford University for serological investigation. Eight days after his entrance into the hospital the urticarial rash extended over the chest and abdomen and persisted for four more days. The sedimentation rate was 18 mm on admission, went as high as 28 mm during the first month of illness and gradually receded to 13 mm two weeks before discharge.

Serial roentgenograms of the chest revealed a gradual resolution of the original parenchymal infiltration until June 7, approximately three weeks after admission when evidence of bilateral infiltration was noted. This too showed gradual clearing until June 23 when a new area of infiltration was seen in the second right interspace. At about this time the white blood cells rose to 14,100 with 31 per cent

eosinophiles Following this there was a gradual clearing of the involved areas and on discharge the roentgenogram was considered essentially negative Sputum examinations revealed no coccidioidal spherules on wet slide preparation, but culture on Sabouraud's media gave a growth suggestive of *Coccidioides immitis*, which was subsequently proved by animal inoculation Repeated examinations of 12 specimens of sputum failed to reveal any tubercle bacilli on either smear or culture Stools were negative on repeated occasions

Serological tests performed June 26, 1943, were as follows

Complement Fixation Negative in all dilutions

Precipitin Tests Serial Dilutions of Antigen

|           |      |      |
|-----------|------|------|
| Undiluted | 1 10 | 1 40 |
| ++++      | ++++ | ++   |

These results were interpreted as characteristic of a primary coccidioidal infection as yet well focalized

Approximately two months after admission the patient was given modified ambulatory privileges He continued to remain afebrile and asymptomatic and was gradually allowed to extend his activities in the Army Air Forces Rehabilitation Program He was subsequently sent to duty on August 3, 1943, after approximately 80 days of hospitalization and after fulfilling all the criteria for return to duty

This patient was observed for approximately three months after his return to duty from the hospital, and during this time repeated physical examinations and chest films were essentially negative Sedimentation rates and leukocyte counts were within normal limits He had no complaints and is now doing full duty

#### PLEURISY WITH EFFUSION

Pleurisy with effusion occurred in five, 5 per cent, of the cases This complication was seen in three white patients and two colored patients, or in 6 per cent of the white group and 4 per cent of the colored group The effusion, with one exception, occurred early in the course of the acute phase of the disease Three of the effusions were present on admission, one occurred 15 days after hospitalization, and the fifth came on approximately five months after cavity formation Although four of the five cases had massive effusions, there was no evidence of respiratory embarrassment Thoracentesis was done on these four cases of effusion, and what fluid was not withdrawn was rapidly absorbed

Examination of the fluid removed from the chest revealed a specific gravity in keeping with an exudate (1.022), and a marked preponderance of lymphocytes Smear and culture with guinea pig inoculation was done routinely, and the fungus was recovered in one patient

The following is a case of pleurisy with effusion

This patient was admitted to the hospital on June 22, 1943 Skin test for coccidioidomycosis on June 12 was negative but was two plus on June 19, 1943 During the course of the epidemiological studies he was discovered to have a white blood cell count of 18,400 with 5 per cent eosinophiles His sedimentation rate was 16 mm and chest roentgenogram was reported as showing increased prominence and hazy density about the right hilum with generalized increase in the markings, more pronounced in the right lower lung field There was also hazy density with irregular and poorly defined borders in the right costophrenic angle

Because of the above findings, the patient was admitted to the hospital for treatment. On entrance the patient stated he had experienced some mild right-sided chest pain for the past two weeks and night sweats and fever for the past week. Physical examination revealed a well developed, well nourished, white male of 21 who was not acutely ill. His temperature on admission was 99.2° F, and examination of his chest revealed no abnormal findings except for slight suppression of breath sounds at the right base.

The patient was put on symptomatic therapy including bed rest, and except for a slight amount of fever, got along fairly well until July 7, his fifteenth day of hospitalization, at which time physical examination revealed evidence of a right-sided pleural effusion. This was confirmed by roentgenogram. At this time the white blood cell count was 12,000 with 9 per cent eosinophiles and the sedimentation rate rose to 30 mm. On July 22, about two weeks after the effusion was first noted thoracentesis was done, with the removal of 600 c.c. of a straw-colored fluid. Smear of this fluid revealed spherical bodies with endospores typical of *Coccidioides immitis*. This was subsequently confirmed by culture and animal inoculation.

Repeated sputum examinations for *Coccidioides immitis* and tubercle bacilli were negative. Serological tests for *Coccidioides* gave the following results on June 25, 1943:

|                     |           |      |
|---------------------|-----------|------|
| Complement Fixation | 1 2       | 1 4  |
|                     | ++        | +    |
| Precipitin Tests    | Undiluted | 1 10 |
|                     | ++++      | +    |

Interpretation: Findings characteristic of primary coccidioidal infection as yet well focalized.

Following thoracentesis the patient made a gradual and uneventful recovery. Roentgenograms of the chest showed a gradual clearing of the parenchymal lesion and absorption of the remaining fluid. Sedimentation rate returned to normal on August 9, and eosinophilia went down to 2 per cent before return to duty.

On August 17, serologic tests were repeated with the following results:

|                     |                           |     |
|---------------------|---------------------------|-----|
| Complement Fixation | 1 2                       | 1 4 |
|                     | +++                       | +   |
| Precipitin Tests    | Negative in all dilutions |     |

Interpretation: This indicates a definite trend toward complete recovery.

The patient was returned to duty on September 15, 1943, with chest films reported as negative and all criteria for discharge fulfilled. Patient was observed in our Chest Clinic for three months after return to duty, and during this time he had no complaints. The sedimentation rate remained normal, and serial films of the chest were negative.

### DISSEMINATION

As was previously mentioned, dissemination occurred in four of the colored patients, and did not occur in any of the white soldiers. Of the four cases, one terminated in death, one disseminated to muscle, one to bone, and one to both muscle and bone.

The muscle lesions occurred as small, firm, relatively painless intramuscular nodules about one to two months after the onset of symptoms. Bone lesions, on the other hand, were introduced by the sudden onset of pain and tenderness over the involved area. These occurred approximately three to four months after hospitalization.

The following is a case of dissemination to muscle.

A well developed, well nourished, colored male of 28, entered the hospital on May 21, 1943 complaining of headache, cough, chills, and fever of four days' duration. Patient was a laborer with a unit that had worked on construction in the desert area from April 24 to May 14. On admission his temperature was 102.8° F, with respiration rate of 22 and pulse of 96. Physical examination revealed occasional moist râles and increased breath sounds at right base. Roentgenograms of the chest revealed infiltration of moderate density over the lower half of the right lung field. The white blood cell count was 16,100 with 74 per cent polymorphonuclears, 21 per cent lymphocytes, and 5 per cent eosinophiles.

Because of the sudden onset with headache, cough, chills, and fever, accompanied by a high white blood cell count and roentgen-ray findings of infiltration, the patient was put on sulfadiazine therapy. This was discontinued in 48 hours when he showed no response to clinically effective blood levels, and because skin test for coccidioidomycosis was positive (two plus) in 1:100 dilution. At no time did he appear toxic in spite of a swinging type of temperature curve suggestive of a bacterial infection.

On June 7, 1943, he was given a 250 cc blood transfusion from a convalescent case of coccidioidomycosis with moderately high titer in serological studies. On the following day a transfusion was given from another convalescent patient also with moderately high titer. No particular or specific benefit accrued as a result of these transfusions insofar as we were able to determine. He continued to run a swinging febrile course for 41 consecutive days, following which he remained essentially afebrile except for an occasional rise to 100° F.

On June 28, 1943, the patient developed a small pea-sized subcutaneous nodule on the lateral aspect of the left lower leg. Biopsy revealed evidence of an acute inflammatory reaction of undetermined etiology. On July 14, a one-half centimeter firm, non-tender nodule developed in the left deltoid muscle. Biopsy of this nodule revealed typical spherules containing endospores.

Serial roentgenograms of the chest revealed an extension of the original inflammatory process in the right middle and lower lobes during the first 10 days of hospitalization, and then a gradual clearing of the process. Sputum examination revealed typical coccidioidal bodies on June 10, some 21 days after entrance into the hospital. In the early stages of the disease the white cell count reached a height of 19,600, and after a short period of fluctuation it came down to 9,500 with 3 per cent eosinophiles. His sedimentation rate remained about 38 mm throughout most of his hospital stay.

Serological examinations were made at frequent intervals and showed the following:

On June 7, 1943

|                     |           |
|---------------------|-----------|
| Complement Fixation | 1:2       |
|                     | +++       |
| Precipitin Tests    | Undiluted |
|                     | +++       |

Interpretation: Findings indicate a primary coccidioidal infection as yet well localized.

On June 14, 1943

|                     |       |      |      |
|---------------------|-------|------|------|
| Complement Fixation | 1:2   | 1:4  | 1:8  |
|                     | +++   | ++   | +    |
| Precipitin Tests    | 1:100 | 1:10 | 1:10 |
|                     | +++   | ++   | +    |



Interpretation Findings characteristic of primary coccidioidal infection as yet well focalized (Titer slightly higher than previous specimen, but not alarmingly so)  
On July 27, 1943

## Complement Fixation

|      |      |      |      |      |      |       |
|------|------|------|------|------|------|-------|
| 1 2  | 1 4  | 1 8  | 1 16 | 1 32 | 1 64 | 1 128 |
| ++++ | ++++ | ++++ | ++++ | ++++ | +++  | +     |

## Precipitin Tests

|           |      |      |
|-----------|------|------|
| Undiluted | 1 10 | 1 40 |
| ++++      | ++++ | +    |

Interpretation The titer of complement fixation is now in the range of disseminated infections

A titrated skin test at this time showed the following

| Dilution | 24 hrs Positive                           | 48 hrs Positive                |
|----------|---|--------------------------------|
| 1 1,000  | $\frac{3}{4}$ " diam                      | 1" diam                        |
| 1 100    | $\frac{3}{4} \times 1$ " diam             | $1\frac{1}{2}$ " diam          |
| 1 10     | $1\frac{1}{2} \times 2\frac{1}{2}$ " diam | $2\frac{1}{2} \times 3$ " diam |

On Aug 13, 1943

|                     |           |      |      |      |      |      |
|---------------------|-----------|------|------|------|------|------|
| Complement Fixation | 1 2       | 1 4  | 1 8  | 1 16 | 1 32 | 1 64 |
|                     | ++++      | ++++ | ++++ | ++++ | ++++ | +++  |
| Precipitin Tests    | Undiluted |      | 1 10 |      |      |      |
|                     | ++        |      | ++++ |      |      |      |

Interpretation The titer of complement fixation continues to rise, indicating that dissemination is also continuing

This patient remained in the hospital until September 9, 1943, representing 111 hospital days, during which time he developed another subcutaneous nodule in the right epitrochlear region. He was transferred to a Veterans Facility for further care. A letter from this Facility stated that the patient was discharged on October 13 after an uneventful and asymptomatic hospital course. A roentgenogram of the chest taken during his hospitalization at the Veterans Facility showed further resolution of the inflammatory process in the right lower lobe. His sedimentation rate was reported as 9 mm. The eventual outcome of this patient will be of interest.

The following is a fatal case of disseminated or progressive coccidioidomycosis with autopsy.

A well developed, well nourished, colored male of 21 years, entered the hospital on March 25, 1943, because of precordial pain and palpitation of two weeks' duration, and chills, fever, and cough of two days' duration. Examination revealed a temperature of  $101.4^{\circ}$  F (orally), pulse 22, respirations 22. The pharynx was moderately injected and the breath sounds were roughened over the right base where an occasional transient rale could be heard. There were no other abnormal physical findings.

His white blood cell count on admission was 8,900 with 66 per cent polymorphonuclears, 30 per cent lymphocytes, 4 per cent eosinophiles, and 1 per cent monocytes. Chest film revealed an increase in density along the right upper mediastinum in the first and second interspaces suggesting a possible primary atypical pneumonia. An electrocardiogram was normal except for an inverted T-wave in Lead IV. A tentative and questionable diagnosis of primary atypical pneumonia was made although tuberculosis, fungus infection, and early Hodgkin's disease were considered and had to be ruled out. Several sputum examinations for significant organisms were entirely negative.

The patient was put on symptomatic therapy and continued to show a septic temperature ranging from 99° to 103° F. daily. Coccidioidin skin tests were negative in 1:1,000 and 1:100 dilutions on repeated occasions. Tuberculin skin tests using O.T. tuberculin in a strength of 1:10,000, 1:1,000, and 1:100 were also negative.

During his illness the patient was given a course of sulfadiazine and sulfathiazole therapy with no response. He also received three blood transfusions from patients convalescing from primary atypical pneumonia, but none of them had any effect on his clinical course. During all this time the patient clinically did not appear to be as sick as his temperature curve indicated.

Meanwhile, his white blood cell count rose from 8,900 with 3 per cent eosinophiles on entrance, to 16,300 and 26 per cent eosinophiles. Serial chest films showed an infiltration extending into the third right interspace anteriorly with marked increase in prominence and density about the right hilum and gradual infiltration into the right apex.

On April 10, 1943, numerous small discrete subcutaneous nodules developed over the trunk. Similar nodules of a larger size developed on the medial surface of the left lower extremity. None of these was painful, all were firm and seemed to be attached to or a part of the underlying tissue. There also appeared some small pustular lesions on the face.

By this time the patient was beginning to bring up a moderate amount of sputum, and examination of this sputum revealed the spherules of *Coccidioides immitis*. At this time also a skin nodule was biopsied and revealed the presence of *Coccidioides* as proved by culture and guinea pig inoculation, as well as by pathological section of the material removed.

The patient became progressively worse, his temperature ranged from 104° to 105° F. daily, and the respiratory rate rose to 50 per minute. On April 22, 1943, a portable roentgenogram of the chest revealed a marked extension of the pneumonic process involving almost all of both lung fields. The nodular type of increased density in the right upper and middle lobe showed a tendency to become confluent so that complete consolidation was present. Consolidation was also present in the left lung from the apex to the fourth interspace. Despite active supportive therapy the patient became moribund and died on the twenty-ninth day of hospitalization.

**Autopsy.** *General.* The body showed good muscular development and nutrition. Scattered throughout the subcutaneous tissues of the face, scalp, and extremities were firm and at times fluctuant nodules measuring three to five millimeters in diameter. There were most numerous on the face and scalp where some of them had broken down and discharged their contents. Similar nodular masses were palpated in the muscles. The lymph nodes of the axillae and groin were enlarged and firm. There was a fluctuant mass in the region of Virchow's node which measured 1.2 cm. in diameter.

*Respiratory System.* In each pleural cavity there were 500 cc. of straw-colored fluid. The pleura was glistening throughout. Both lungs were dark purple in color with many, though firm, slightly round nodules scattered over the surface. The lungs, cut with care, the cut surface showed patchy areas of consolidation. The surrounding parenchyma was congested and frothy blood-tinged edema fluid could be expressed from the surface. Anteriorly both lungs were crepitant to palpation. The bronchi contained frothy edematous fluid. The tracheobronchial lymph nodes were markedly enlarged, the largest measuring 2 by 3 by 5 cm. On section they were composed of necrotic granular material.

*Spleen* The spleen was markedly enlarged, weighed 700 grams, and measured 11 by 15 by 6 cm. It was quite soft on palpation and pulp oozed from the cut surface. Scattered over the capsular and cut surface were the same small yellowish necrotic nodules. The trabecular structure and malpighian bodies were indistinguishable.

*Liver* The liver weighed 2,470 grams. The surface was completely covered with nodular areas similar to those seen in other organs. On section they were found scattered throughout the parenchyma which was congested.

The gall-bladder, biliary duct system, pancreas, and adrenals were grossly normal.

*Genitourinary Tract* The right kidney weighed 285 grams and the left 240 grams. Their capsules stripped with ease, revealing the same scattered miliary abscesses. On section the cortical and pyramidal markings were distinct except where obliterated by the small abscesses.

The pelvis, ureters, bladder and testicles were grossly normal.

*Skull and Central Nervous System* On removing the scalp the above mentioned abscesses were found to lie in the subcutaneous tissues and did not involve bone. The dura mater, dural sinuses, and arachnoid membrane were normal. There was congestion of the cerebral vessels. The convolutions of the brain were flattened and the sulci obliterated. No other pathological change was found in the brain.

*Muscles* Many of the above mentioned subcutaneous abscesses extended down to involve the fascia and the underlying muscle.

*Microscopic Examination Lungs* All sections of the lung showed scattered areas of fairly dense fibrous tissue which were irregular in size and shape. Some of these resembled tubercles in their structure, having a central area of epithelioid cells surrounded by a wide zone heavily infiltrated with round cells, macrophages, and at times polymorphonuclear cells. In many of these areas, there were seen large spherical bodies, having a diameter of 10 to 18 micra, a thick hyaline capsule, and a large central zone filled with small endospores. These bodies were typical of *Coccidioides immitis*. The surrounding parenchyma showed thickening of the alveolar septa due to infiltration of round cells and macrophages and some increase in fibrous tissue. Many of the alveoli contained large numbers of macrophages and a few were filled with purulent exudate. A number of the alveoli showed partly hyalinized plugs in the process of organization. Similarly many of the small bronchioles were filled with plugs of well organized fibrous tissue which was infiltrated with round cells and macrophages and occasionally the specific organism.

Microscopic sections through the heart, spleen, liver, adrenals, kidneys, and lymph nodes showed similar scattered areas which were pathologically similar and varied only in size and numbers. This consisted of a central area of necrosis, surrounded by an inflammatory zone infiltrated with round cells and macrophages and accompanied by a minimal fibrotic reaction. The organism of *Coccidioides immitis* could be demonstrated in many of these granulomatous nodules.

*Pathological Diagnosis* 1 Coccidioidomycosis, disseminated, with abscesses of the lungs, spleen, liver, kidney, adrenals, lymph nodes, subcutaneous tissue and muscle. 2 Pneumonitis, diffuse, organizing. 3 Congestion, passive, generalized.

### SUMMARY

Reference to the tabulation of end results shows the disease to be preponderantly more severe in colored persons. The hospital days were high, a finding in keeping with most others reporting on the subject. The number of hospital days in colored soldiers was almost twice that of white soldiers.

We should be remiss if we failed to mention the Convalescent and Rehabilitation Program of the Army Air Force Hospitals. This was of dis-

TABLE V  
Summary of Complications and End Results in 100 Cases Hospitalized for  
Pulmonary Coccidioidomycosis

|                              | White | Colored | Total |
|------------------------------|-------|---------|-------|
| Total Cases                  | 51    | 49      | 100   |
| Cavitation                   | 2     | 4       | 6     |
| Effusion                     | 3     | 2       | 5     |
| Dissemination                | 0     | 4       | 4     |
| Death                        | 0     | 1       | 1     |
| Separated from Service       | 2     | 4       | 6     |
| Hospital Days (Case Average) | 55.7  | 99      |       |
| Hospital Days                | 2832  | 4846    | 7678  |

tinct benefit to both patients and doctors in such a long term hospitalization program

1. A new endemic area in Southern California has been reported for *Coccidioides immitis*.

2. A series of 100 cases of acute pulmonary coccidioidomycosis has been reported with end results as far as observed over one year

3. Complications and illustrative cases have been presented

#### BIBLIOGRAPHY

1. BAKER, E. E., and MARK, E. M. Spherule formation in culture by *Coccidioides immitis*, Rixford and Gilchrist 1896, Am Jr Trop Med, 1941, xxi, 589-595
2. CARTER, R. A. Infectious granulomas of bones and joints, with special reference to coccidioidal granuloma, Radiology, 1934, xxiii, 1
3. CARTER, R. A. The roentgen diagnosis of fungus infections of the lungs, with special reference to coccidioidomycosis, Radiology, 1942, xxxviii, 649
4. COLEMAN, J. R. Roentgenological types of pulmonary lesions in primary coccidioidomycosis, Am. Jr Roentgenol, 1944, i, 1-8
5. DAVIS, B. L., SMITH, R. T., and SMITH, C. E. An epidemic of coccidioidal infection, Jr Am Med Assoc, 1942, cxviii, 1182-1186
6. DICKSON, E. C. Valley fever, California and West Med, 1937, xlvii, 151-155
7. DICKSON, E. C., and GIFFORD, M. A. *Coccidioides* infection (coccidioidomycosis), Arch. Int. Med, 1938, lvi, 853-871
8. EMMERT, C. W. Coccidioidomycosis in wild rodents, Pub Health Rep, 1943, lvm, 1-5
9. EMMERT, C. W. Isolation of coccidioides from soil and rodents, Pub Health Rep, 1942, lvi, 109-111
10. EMMERT, C. W., and ASHMAN, L. I. The isolation of *Haplosporangium parvum* N. Sp. and *Coccidioides immitis* from wild rodents, Pub Health Rep, 1942, lvi, 1715-1727
11. FAY, H. K., SMITH, C. E., and DICKSON, E. C. Acute coccidioidomycosis with erythema multiforme in children, Jr Pediatr, 1939, xv, 163-171
12. GORDON, M. A. San Joaquin fever. Annual Report Kern County Health Department for the Fiscal Year July 1, 1935 to June 30, 1936, pp 22-23
13. GORDON, D. M., and FORD, S. Primary pulmonary coccidioidomycosis, War Med, 1943, xxi, 117

- 17 MEYER, K F Discussion of paper by DICKSON, E C. Valley fever, California and West Med, 1937, xlvii, 155
- 18 OPHULS, W Further observations on a pathogenic mould formerly described as a protozoan (*Coccidioides immitis*, *Coccidioides pyogenicus*), Jr Exper Med, 1905, vi 443
- 19 OPHULS, W, and MOFFITT, H C A new pathogenic mould, Philadelphia Med. Jr, 1900, v, 1471-1472.
- 20 PEERS, R. A, HOLMAN, E E., and SMITH, C E. Pulmonary coccidioidal disease, Am Rev Tuberc, 1942, xlv, 723-740
- 21 POSADAS, A Un nuevo caso de Micosis fungoidea con psorospermias, An de cir (Argentina), 1892, xv, 585 (Reference from MOORE, M Blastomycosis, coccidioidal granuloma and paracoccidioidal granuloma, Arch. Dermat and Syph, 1938, xxxviii, 163-190)
- 22 RIVFORD, E A case of protozoic dermatitis, Occidental Med Times, 1894, viii, 704-707
- 23 SMITH, CHARLES E An epidemiological study of acute coccidioidomycosis Proceedings of the epidemiology section of the Sixth Pacific Science Congress, 1939, v, 797-809
- 24 SMITH, CHARLES E Epidemiology of acute coccidioidomycosis with erythema nodosum, Am Jr Pub Health, 1940, xxx, 600-611
- 25 SMITH, CHARLES E Coccidioidomycosis, Med Clin N Am, 1943, xxvii, 790-807
- 26 SMITH, CHARLES E Parallelism of coccidioidal and tuberculous infections, Radiology, 1942, xxxviii, 643-648.
- 27 SMITH, CHARLES E Personal communication
- 28 SMITH, CHARLES E Report of coccidioidomycosis study in the year 1942-1943 Preventive Medicine Division, Office of the Surgeon General, United States Army
- 29 SMITH, CHARLES E., and BAKER, E E A summary of the present status of coccidioidal infection, Bulletin, Calif State Dept Pub Health, 1941, xx, 113-115, 117-118
- 30 STEWART, R A, and MEYER, K F Isolation of *Coccidioides immitis* from the soil, Proc Soc Exper Biol and Med, 1932, xxx, 937-938
- 31 WERNICKE, R Ueber einen Protozoenbefund bei Mycosis Fungoides, Centralbl f Bakt, 1892, xii, 859-861
- 32 WINN, WILLIAM A Pulmonary cavitation associated with coccidioidal infection, Arch Int Med, 1941, lxxiii, 1179
- 33 WINN, WILLIAM A, and JOHNSTON, GILBERT H Primary coccidioidomycosis a roentgenological study of 40 cases, Ann Int Med, 1942, xvii, 407

# THE PATHOLOGY OF SICKLE CELL DISEASE

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THE incidence of the sickle cell trait among North American Negroes has been estimated from various surveys to be 7 per cent,<sup>23</sup> 7.2 per cent,<sup>10</sup> 9.1 per cent<sup>6</sup> and even as high as 13 per cent<sup>1a</sup> of the Negro population. Clinical sickle cell disease appears in an undetermined fraction of cases in which the trait is present, estimates of this ratio varying from 1.7 to 1.40.<sup>23</sup> As far as can be determined the trait is transmitted as a true Mendelian dominant,<sup>12, 15, 23, 33</sup> independent of the inheritance of blood type.<sup>23</sup> This apparent fact has been used as an argument that the trait is limited exclusively to Negroes, and that sickle cell anemia in white persons<sup>21, 21</sup> is pathognomonic of Negro ancestry.<sup>23</sup> There is some evidence, however, that this disease may have existed in Mayan Indians,<sup>20</sup> which suggests the possibility that the mutation responsible for the abnormality may be capable of repetition independently in another race. In any case the estimated 135,000 sufferers from the disease in the United States are almost entirely Negroes.<sup>24</sup>

The disease exhibits a chronic hemolytic anemia which is usually manifested by acute exacerbations superimposed upon relatively quiescent periods.<sup>1, 2, 13</sup> These episodes are characterized by severe joint, muscle and abdominal pains, fever and other constitutional symptoms, and massive hemolysis with jaundice.<sup>2</sup> The mechanism of these hemolytic crises has not been determined. A search of the literature has disclosed no reported case in which the crises were studied over a period of time adequate to establish their characteristics and periodicity.

The purpose of the present paper is to describe the pathology of sickle cell disease and to outline a concept of the mechanism underlying the development of the hemolytic crises.

We studied a patient with sickle cell disease for 12 months, 30 weeks at St. Luke's Hospital and the remainder of the time at Goldwater Memorial Hospital. This case presented in all respects the characteristics typical of sickle cell disease as described in the literature. Investigations of the behavior of the erythrocytes have been reported in a previous communication.<sup>25</sup>

rheumatic fever since the age of three years, and he had been in bed for seven weeks previous to admission because of the symptoms which eventually brought him to the hospital

He was rather slight, but otherwise not remarkable in general appearance. The mucous membranes, palms, and soles were pale. Increased pulsations were evident in many of the peripheral arteries, especially about the ramus of the jaw. The patient appeared in moderate discomfort, with pains in both ankles, the calves, right shoulder, anterior chest, and back. The temperature was normal, but the pulse rate was 120. The heart appeared slightly enlarged to the left, with a somewhat forceful apical impulse 11 cm from the mid-line in the fifth left interspace. There was a blowing systolic apical murmur and a suggestion of a presystolic murmur, neither of which was well transmitted away from the apex. The rhythm was regular and the other sounds were of good quality. The lungs were clear. The spleen could not be felt but the liver was enlarged 2 to 3 cm below the costal margin. Some tenderness was found about the affected joints, and in the calves and muscles of the thighs and shoulders. There were several small dark scars on the shins, presumably remnants of old healed ulcers. There were no gross bony deformities except for the fifth fingers of both hands, which were shortened, owing to dwarfed metacarpals. The sclerae and the contour of the retinal vessels showed none of the abnormalities previously described in sickle cell disease<sup>14, 16</sup>

The first blood count after admission established the diagnosis of sickle cell disease. During the first 10 days the clinical picture continued unchanged, with a low grade fever and migratory pains. Thereafter the patient's course was characterized by the so-called "active" and "latent"<sup>25</sup> phases alternately of sickle cell disease. Altogether there were seven "active" periods. Five of these were very similar in type, and occurred in the form of dramatic crises. The remaining two assumed a less striking pattern, resembling more the picture of activity presented during the first 10 hospital days. Of the total number of 214 days spent at St. Luke's Hospital, 79 were manifested by obvious activity of the disease, and 135 days were apparently "quiescent." The illness was thus actively manifested 36.9 per cent of the time. During the quiescent periods the patient was clinically quite unremarkable. He appeared simply as a frail young man with the physical signs delineated above, who was moderately active and who carried trays and did useful chores about the ward.

The typical crisis (of which there were five) would start suddenly, so that within the space of about two hours, the patient would be transformed from a cheerful and active young man into a victim of very severe and widely disseminated joint and muscle pains. As these pains commenced the patient would lie on his bed with his extremities in semiflexion, and protest against all attempts to move him. The pain was so severe that morphine in  $\frac{1}{4}$  grain (0.15 gm) doses repeated every three or four hours usually afforded only slight relief during the first two or three days. There was marked tenderness in the various painful regions, most frequently in the anterior thigh muscles, knee joints, shoulders, and right hip, but occasionally also about the thorax. Although abdominal pain sometimes occurred, there was never acute abdominal tenderness and spasm, or nausea, vomiting, and diarrhea, to suggest the well known "abdominal crises"<sup>26</sup> of this disease.

Pain was in every case the first symptom of a crisis. It was invariably followed by a rise in temperature commencing 4 to 24 hours later, the average duration of this febrile interval being 16½ hours. The peak of the fever would usually be reached within 24 hours of its onset. Despite its frequently rapid rise, it was never associated with a chill. By the third to the fifth day the pain and temperature would begin to subside together. The first sign of remission was usually the observation that morphine succeeded in relieving the pain. At about the same time the temperature would start to recede, and the patient would steadily improve thereafter. By about the

eighth day the crisis was over, and by the tenth to eleventh day the patient would usually be up helping about the ward again

The above described pattern represents the clinical behavior of five crises which were so strictly similar that they may be taken to represent the "typical" crisis. There were two other crises of less sharply defined pattern in which the only constant clinical feature was the precedence of fever by pain. Also there were occasional periods of ill defined activity, such as the first 10 hospital days, and three other attacks of pain with or without slight fever, lasting from a few hours to one day.

The asymptomatic periods between the crises lasted from 10 to 27 days, the average intercritical period being 16.7 afebrile days. On the average a crisis would start every 26½ days, the extreme intervals between their onset being 20 to 36 days. The crises lasted for from 7 to 10 days, the average duration of the seven reported crises being 8.4 days. Two crises merged into moderately extensive though relatively symptomless episodes of pulmonary consolidation which we believe to have been caused by infarcts. These were accompanied by fever and slight cough, but otherwise did not bother the patient. The last, and severest crisis, was complicated also by congestive heart failure and gross pulmonary edema, so that for two days it appeared that the patient would not survive.

A typical crisis began on February 3, 1943. The associated laboratory findings are illustrative of all the crises studied, both typical and atypical. The clinical course lasted eight days and was as described above. Throughout almost daily determinations the hemoglobin and red blood cell levels were seen to fall gradually throughout the crises from 10.6 gm per 100 cc and 3.0 million red blood cells to 7.7 gm and 2.1 million red blood cells respectively. One week later these levels had recovered to 9.5 gm and 2.9 million respectively, and by the end of the third week (near the beginning of the next crisis) the values were fully restored, being 10.8 gm and 3.5 million respectively. These last figures represent the "peak" values for this patient, as his erythrocytes never rose any higher. The serum icterus index became elevated during the crisis. On the first day of the crisis its value was 8. On the third and eighth days it was 20. Two days after the end of the crisis it had returned to a reading of 10. Although the icterus index often ranged between 18 and 20 even during the quiescent periods, it regularly rose higher during the crises. During two severe crises the patient was grossly jaundiced.

Hemolysis during the last crisis observed by us was so rapid and severe that in the space of six days the hemoglobin dropped from 10.3 gm per 100 cc of blood to 6.6 gm, and the red blood count from 3.4 to 2.1 million per cu mm. This is a destruction of 36 per cent (from the fall in hemoglobin) or 38 per cent (from the fall in red blood cells) of the total erythrocyte elements of the body in six days, an average of 6 per cent of the body's red cells being destroyed per day.

The erythrocyte sedimentation rate showed no significant variation from normal during the crises except for two high values of 76 and 110 respectively in the first two weeks, the maximum normal being 20 mm per hour.

The leukocyte count increased from 8,850 per cu mm with a differential count of 41 per cent polymorphonuclear leukocytes and 51 per cent lymphocytes during an attack, e. g., to 19,000 with 89 per cent neutrophils during one crisis and 34,000



did not sickle. Blood smears showed other manifestations of immaturity, such as diffuse and stippled polychromatophiles and Howell-Jolly bodies. The leukocytes, in addition to becoming elevated with each crisis, reflected bone marrow stimulation in a very marked regenerative shift to the left. On several occasions myelocytes appeared. During the last recorded crisis true myeloblasts were found in large numbers on three successive blood smears. These reached a concentration of 7 per cent of a white count of 22,000.

An apparent increase in the number of sickle cells was observed in chamber counts near the beginning of each crisis. Direct smears made of both arterial and venous bloods during a quiescent phase showed that 5.4 per cent of the red cells were sickled, and, on the first day of a crisis that 10 per cent were sickled, the venous blood showing slightly more deformed cells by this method than the arterial. Although this method is crude, it appears to yield useful results in that the arterial and venous smears were within fairly close limits on each determination. Thus for the first count the arterial blood showed 48 abnormal forms in 1000 cells and the venous 56. In the second the figures were arterial 91 sickled cells, venous 116.

The hematocrit value, which was 30.5 per cent of packed red blood cells during the quiescent phase, had dropped to 26 per cent just after a crisis. There was a slight increase in the red cell volume index (1.07-1.1) and decrease of the hemoglobin saturation index (0.98-0.95) at the end of a crisis. These variations may be within the limit of laboratory error, but they are in any case characteristic. The color index remained constant (1.04) throughout three determinations.

The fragility of the red blood cells to hypotonic saline was reduced during both active and quiescent phases, hemolysis being very imperfect at a concentration which completely hemolyzed the control cells.

The test for urobilin which was constantly present in the urine, was qualitatively increased during the crises. (Quantitative measurements were not undertaken.) Bilirubin was never found in the urine.

A skin and muscle biopsy taken from a tender area in the left anterior thigh on the first day of a crisis, and fixed in formalin, showed capillaries, venules, and arterioles in the muscle to be crowded with, and slightly distended by sickled erythrocytes and a delicate fibrin meshwork.

Other laboratory data are of interest though not related specifically to the crises. Roentgenograms of the skull afforded extraordinary evidence of a chronic hemolytic anemia, in the demonstration of marked thickening of the tables over the vertex and a ray-like 'hair on-end' arrangement of the trabeculae. Spotty decalcification of the long bones was also seen. Roentgenograms of the right hip demonstrated irregularity of the femoral head with flattening and eburnation suggesting aseptic necrosis due to impairment of the blood supply to the region presumably as a result of thrombosis. The chest film showed moderate enlargement of the heart especially in the region of the left ventricle.

The urine consistently showed a few casts and traces of albumin. Signs of kidney insufficiency were revealed in a fairly fixed specific gravity and an inability to concentrate to a higher specific gravity than 1.010. There was also hematuria on at least one occasion.

The blood platelets varied by direct counts between 200,000 and 400,000. The total protein content of the blood was consistently normal. An electrophoretic analysis of the plasma will be discussed later in this paper. The Mazzini blood serological test was negative. The blood levels for urea nitrogen, non-protein nitrogen, and uric acid were not remarkable, being 10.0, 20.0, and 4.5 mg per 100 cc of serum respectively. The vitamin C level of 0.83 mg per 100 cc rose to 1.5 mg following administration of ascorbic acid. The serum alkaline phosphatase was normal, being 3.4 and 4.4 Bodansky units on two determinations. The blood cholesterol was 222.

mg per 100 c c The van den Bergh reaction was direct, positive, delayed. A gastric analysis yielded normal free HCl The serum calcium was 11.4 mg per 100 c c The  $\text{CO}_2$  content of the venous blood was 49 volumes per cent

Electrocardiograms showed progressive T-wave changes throughout the period of hospitalization The first tracing showed no abnormalities other than sinus tachycardia There was a gradually increasing left axis deviation throughout the patient's course, and progressive inversion of the T-waves until they were finally abnormal in four leads There were no significant changes in the P-R interval The changing electrocardiogram reflected progressive cardiac damage which culminated clinically in congestive heart failure and pulmonary edema near the end of the patient's hospital course

Epistaxis was noted on four occasions during the period of observation

Among the therapeutic agents employed, iron and blood transfusions were directed against the anemia, but wholly without success Ferrous sulphate was given in dosages amounting to 1 gram daily for an uninterrupted period of three months, with no demonstrable effect on the red blood elements Two transfusions, each of 500 c c of whole blood, were followed by no change, or a very transient rise, in the hemoglobin and red blood cell count The first of these transfusions was followed by an abrupt temperature rise to  $104^{\circ}\text{F}$ , with a gradual fall to normal over a 48 hr period The second transfusion was given at the height of a crisis, so it is impossible to tell whether or not it caused a similar reaction

In summary, the picture is one of chronic hemolytic anemia of a severe degree, manifesting itself by "active" and "latent" phases Abnormal blood destruction is evident at all times, including the "quiescent" phase, as reflected by the persistent hyperbilirubinemia During one hemolytic crisis 37 per cent of the red blood elements were destroyed in six days Compensatory bone marrow hyperplasia is so far advanced that it accounts for striking roentgenographic findings The chronically elevated reticulocyte count rises further during crises, and large numbers of nucleated erythrocytes are released into the blood stream The crises are also characterized by dramatic onset and course of 8 to 10 days, and by a severe constitutional reaction They are associated not only with blood destruction and regeneration, but also with a high leukocytosis Although the red blood picture as a whole is one of marked poikilocytosis and anisocytosis, the anemia remains strictly normocytic and normochromic Iron would therefore not have a rational basis as therapy There were also noted progressive myocardial damage and renal involvement throughout the patient's course

#### ELECTROPHORESIS STUDY

An electrophoretic analysis of the patient's plasma during a quiescent period demonstrated an A/G ratio of 1.12, excluding fibrinogen The pattern showed that 47.1 per cent of the total protein was albumin, 7.9 per cent alpha, 11.0 per cent beta, and 23.4 per cent gamma globulin, and 10.3 per cent fibrinogen A chemical analysis showed the total protein of the plasma to be 8.8 per cent The low A/G ratio is not uncommon in disease states Longworth, Shedlovsky, and MacInnes<sup>12</sup> have reported low values in a variety of diseases, such as aplastic anemia, rheumatic fever, pneumonia, peritonitis, peritonsillar abscess, acute lymphatic leukemia, lymphogranuloma, obstructive jaundice, hyaline nephrosis, and myeloma It would be interesting to learn whether it is consistently found in sickle cell disease The content of gamma globulin is definitely high, being approximately 50 per cent of

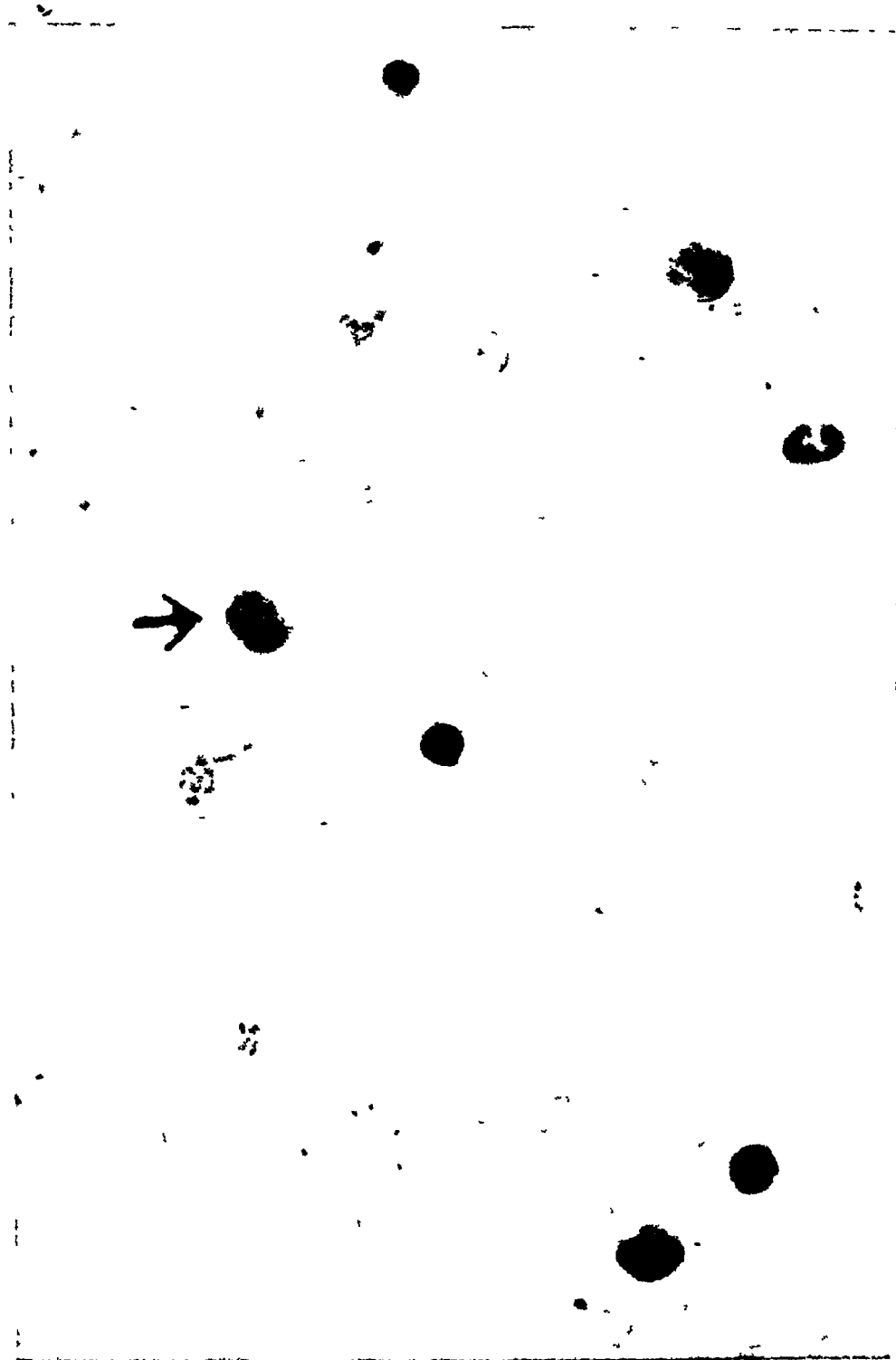


FIG 1 Blood smear obtained during crisis showing myeloblasts. Arrow indicates typical myeloblast. Magnified 1,000 X

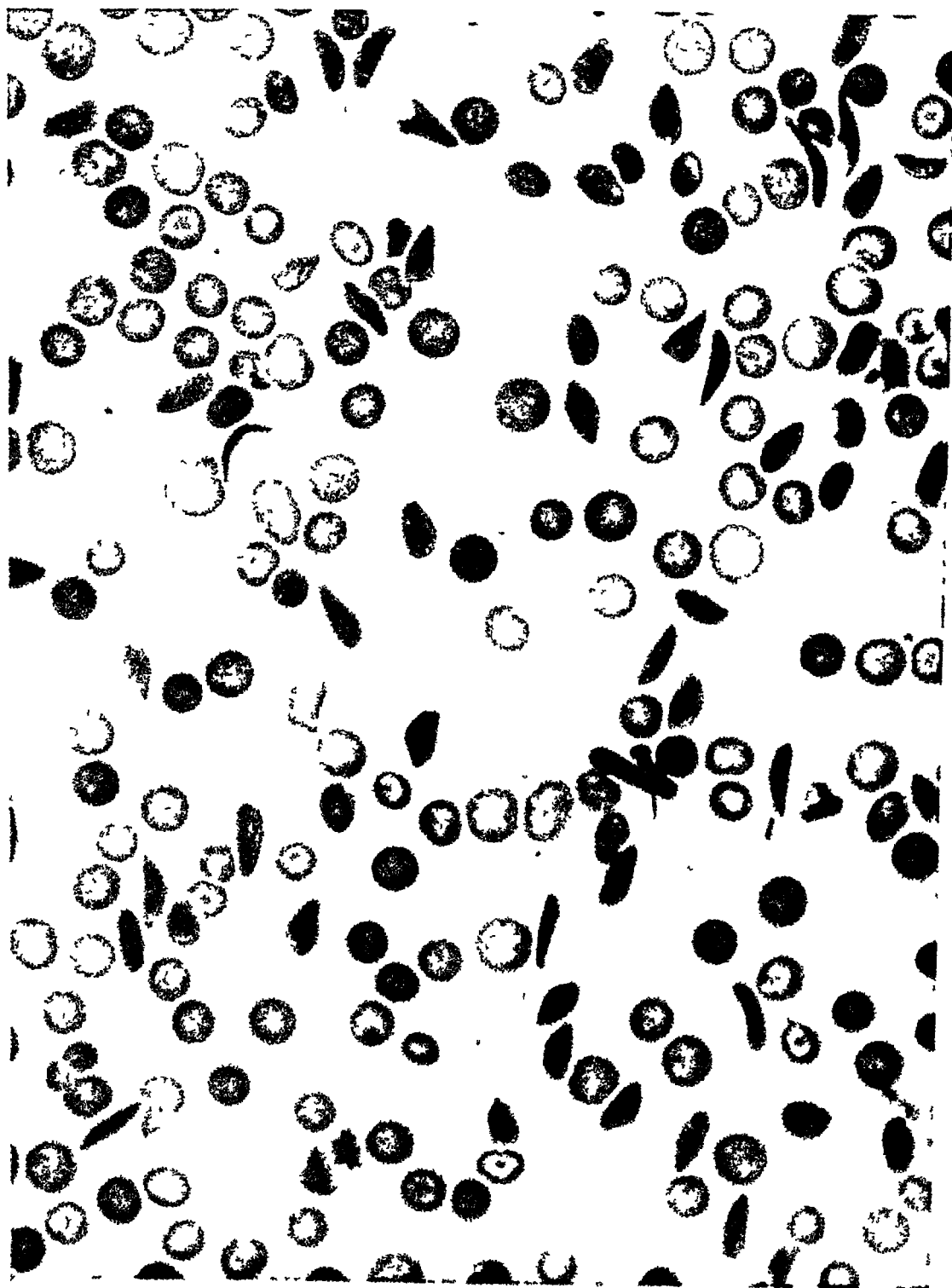


Fig. 2. 122 red blood cells of which 14 during a quiescent period, showing  
abnormal sickle cells

the albumin value, but here also similarly high, relative values for gamma/A were reported by the above authors in aplastic anemia, rheumatic fever, peritonitis and lymphogranuloma

### PROTHROMBIN STUDIES

Prothrombin times of arterial and venous blood were determined according to the method of Shapiro et al<sup>30</sup> All determinations were made in



FIG 3 Biopsy specimen obtained during crisis showing capillary crowded with abnormally shaped erythrocytes including "holly wreath" forms of Sherman and fibrin Magnification 1,000 X

duplicate, and on both whole and 12.5 per cent plasma for each specimen. Controls were run with each determination. As has been described<sup>25-30</sup> a constant relationship was observed between the whole and diluted plasma, and the diluted plasma revealed variations in the prothrombin times in more exaggerated degree than did the whole plasma. There was a total of 44 determinations made on venous blood, 36 of which were accompanied by simultaneous determinations on blood drawn from the radial artery. The average prothrombin time of 14 specimens of whole (undiluted) arterial plasma taken during quiescent periods was 20.1 seconds, the values ranging from 16 to 26 seconds. The average time for the simultaneous 14 venous specimens was 19.3 seconds, the shortest being 16 seconds and the longest 25 seconds. The maximum difference between undiluted arterial and venous blood on any simultaneously drawn specimen was four seconds, and the average difference between these pairs was 1.1 seconds. The corresponding 14 plasma specimens diluted 1:8 with normal isotonic saline averaged 48.1 seconds for arterial blood and 47.8 seconds for venous. The maximum difference between these pairs was six seconds, the average difference being 2.4 seconds. The shortest venous prothrombin time in this group was 42

seconds and the longest 58. The corresponding arterial specimens ranged from 43 to 53 seconds.

It will be seen from these data that there is no constant difference in prothrombin time between arterial and venous blood. It will be seen also that

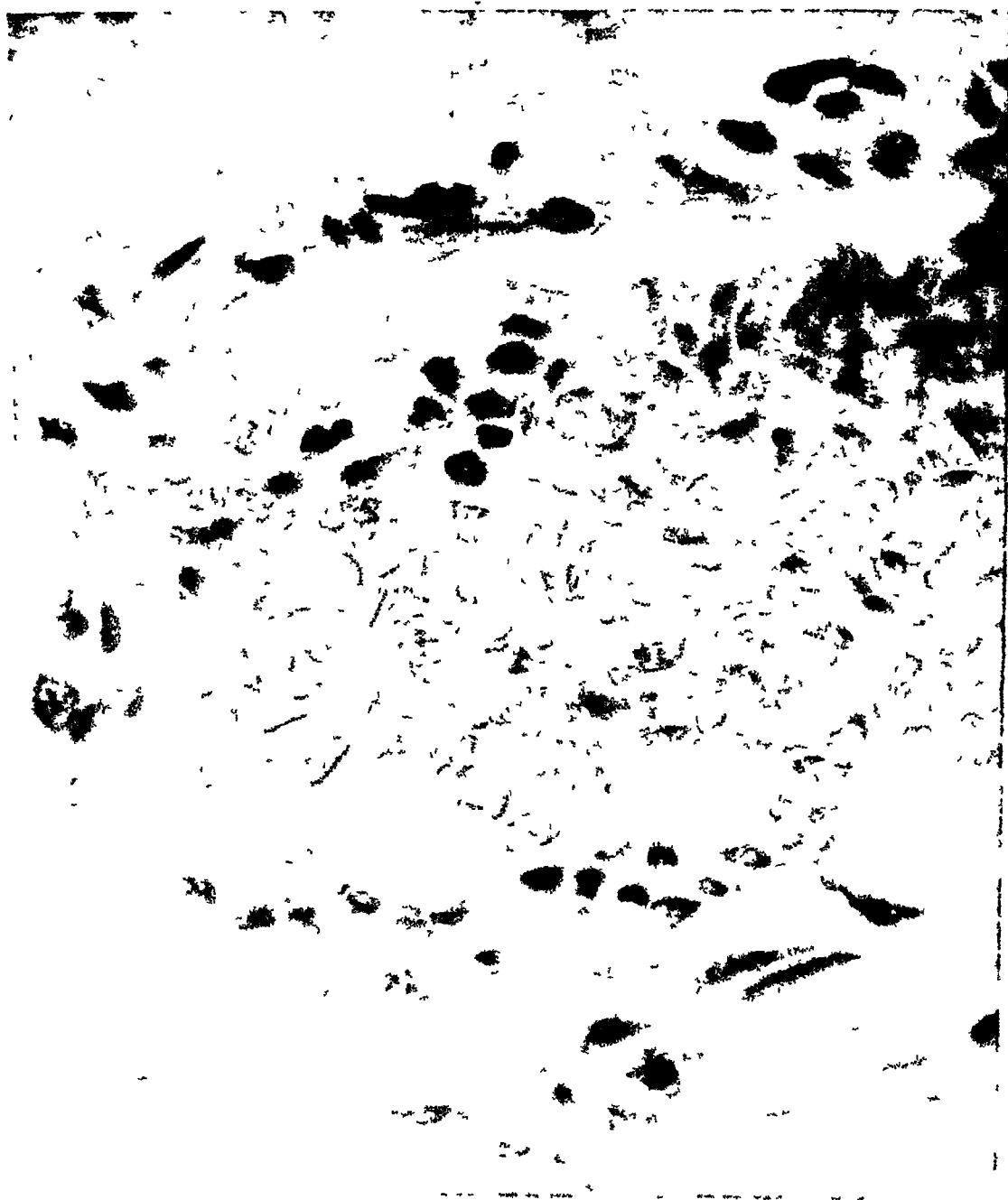


Fig. 1. Blood smear showing a large number of cells (mostly leukocytes) and a few platelets. A note can be made of the presence of a few platelets. Magnification: 1000x.

More prolonged prothrombin times appeared on two occasions (omitting consideration of those taken during anticoagulant therapy), and in both cases these prolonged values heralded the approach of sickle cell crises which appeared within the next 24 hours. Thus before one crisis the values for undiluted plasma were elevated to 36 and 33 seconds (arterial and venous) and for diluted specimens to 73 and 66 seconds respectively. The day before another crisis the undiluted prothrombin times were 26 and 28 seconds while the diluted specimens showed times elevated to 62 and 67 seconds. On both these occasions the prothrombin times had returned to slightly below average



FIG 5 Radiogram of skull. The tables are thickened and the trabeculae present a "hair on end" arrangement.

readings within 48 hours, that is during the early course of the crisis. On the one other occasion in which we happened to make a prothrombin time estimation during the 24 hour period preceding the onset of a crisis no such prolongation was observed. Nevertheless the results indicate a tendency to prothrombin alterations in connection with the crises, and particularly to an increase in prothrombin time immediately before the onset of a crisis. These observations will be referred to below.

#### PATHOLOGY

Attempts at treatment were governed by a consideration of the pathology of sickle cell disease. None of the therapeutic efforts used in the case

presented proved themselves to be indisputably valuable, but they helped to throw some light on pathological processes.

Sickling is a property inherent in the red blood cell and not dependent on external factors<sup>11, 15, ---, 31</sup>. It is precipitated *in vivo* or experimentally by alterations in the ratio of combined to dissociated hemoglobin within the cell<sup>11, 2-, 31</sup>. In the body this alteration depends on the oxygen tension of the



FIG. 2. Red blood cell in solution. The normal red cell is irregular. There is flattening and distortion similar to the picture of cells in disease (asplenic necrosis).

plasma<sup>22</sup>. In the presence of high oxygen tension most of the hemoglobin exists in the combined form as oxyhemoglobin. In this state the red blood cells tend to remain entirely normal in shape and behavior. As the oxygen tension is lowered and the hemoglobin contained in the red blood cell correspondingly dissociated to the reduced form, the cells begin one by one to sickle, and finally experimentally 100 per cent of them can be made to assume a normal form<sup>22, 23</sup>. It appears to be the case that each cell has a



specific threshold, determined by the percentage of its hemoglobin which exists in reduced form, at which it will sickle. Once this threshold is reached sickling is abrupt and almost instantaneous.<sup>22</sup> The process may be reversed by crossing the threshold in the opposite direction. Thus if oxygen is allowed to come into contact with sickled erythrocytes they will immediately revert to the original shape and appear indistinguishable from normal red blood cells.<sup>5, 11, 22, 31</sup> In the circulation sickled forms appear in greatest abundance in the venous circulation, and appear in much fewer numbers in blood simultaneously drawn from arteries, where the oxygen tension is higher.<sup>31</sup> Sickled cells are also found in large numbers in the liver at autopsy<sup>1, 6</sup> and in the spleen at autopsy and at splenectomy.<sup>18</sup> In both these organs the flow of blood may be very slow, and the red blood cells are given the maximum opportunity to discharge their oxygen.<sup>1, 41</sup> We believe that the fibrosis and hemosiderosis characteristic of the spleen in sickle cell disease<sup>1, 3, 6, 13, 10</sup> may be explained by the tendency to stasis of the red blood cell which obtains in that organ. Many of the cells assume sickled form because their hemoglobin becomes dissociated from oxygen, and this factor, together with the stasis, encourages thrombosis of vessels, with infarction and subsequent scarring and contraction.

Before a cell has sickled, or after it has reverted to normal from sickled form, it is essentially indistinguishable from any normal red blood cell. It has an almost jelly-like flexibility and reflects the movements of the fluid medium by gentle undulations and changes in shape. When sickling occurs the cell instantly loses this easy flexibility and appears as fixed and rigid as a crystal of ice as it moves about and abuts against fixed objects.<sup>2-</sup> The end to end length of this form may range from two to five or more times the original diameter of the red blood cell, and there are usually long delicate tapering processes projecting from the ends.

It is inconceivable that such a cell could pass through a capillary so small that it just allows passage of a single file of normal erythrocytes. The sickled form is not only the wrong shape to get through terminal capillaries, but it is also too rigid and unyielding.

That jamming and dilatation of capillaries, sinusoids and small blood vessels with interlocking sickled erythrocytes occur has been repeatedly shown to be the case in many types of tissue.<sup>2, 3, 4, 5, 6, 7, 18, 34, 39, 40, 41</sup> The result of this "capillary blockade" is stasis of blood in the capillaries and small blood vessels and subsequent thrombosis. Thromboses of blood vessels represent the most constant pathological finding in sickle cell disease.<sup>3, 4, 6, 14, 22, 40, 41</sup>

No evidence has yet been advanced that the clinical manifestations of the disease are due to anything other than vascular occlusions on the basis of mechanical obstruction and thrombosis. Even if nothing were known of the mechanics of the disease a review of its clinical manifestations suggests vascular occlusion as the fundamental pathologic change. Both pulmonary<sup>8, 19, 40, 41</sup> and cerebral<sup>2, 3, 19, 32, 34, 35, 40</sup> thrombosis and infarction are



the incidence of true arterial infarction is higher<sup>41</sup> The abnormal cells which emerge in increasing numbers from the venous end of the capillaries easily pass through the large veins to the right heart, and out through the large pulmonary arteries, but as they reach smaller pulmonary vessels their tendency to interlace and conglutinate becomes greater and greater Finally they jam into small vessels and form an impassable meshwork Stasis then occurs and a pulmonary arterial thrombus forms

Stasis due to mechanical obstruction appears to be the primary factor in producing all of the lesions of sickle cell disease As soon as the column of blood becomes static a thrombus forms<sup>24</sup> The hemolytic manifestations of the disease represent for the most part lysis and resolution of these multiple thrombi<sup>1</sup> The fever and other constitutional manifestations of the active phase may be accounted for on the basis of the multiple infarctions The mechanism of the precipitation of hemolytic crises, a subject of considerable speculation,<sup>2, 9, 10</sup> will be discussed below

#### THERAPEUTIC CONSIDERATIONS

Since the crises appear to be intimately associated with multiple thromboses it was felt that anticoagulants had a rationale in therapy If coagulation of the stagnating blood could be prevented long enough to tide the patient over the period of hypersicklemia which presumably initiates a crisis,<sup>1</sup> the severity of the infarctions might be reduced Mechanical blocking of small blood vessels would still occur, but the accompanying widespread thrombosis might be lessened Accordingly dicumarol was administered at the first signs of two successive crises The first of these was "atypical" and the results of therapy difficult to evaluate At about the start of the other crisis, 500 mg of dicumarol were administered within 24 hours The prothrombin time of the whole and diluted (12.5 per cent) plasma was prolonged to a therapeutic level\* within 70 hours after the initial dose However, no significant change was noted in the clinical behavior during this crisis which lasted seven days

The failure to alter the crisis with dicumarol was thought possibly to be related to the long latent period between the administration of dicumarol and the realization of its anticoagulant effect An attempt was made to shorten this period by simultaneous administration of 6 gm of aspirin with the dicumarol, the rationale being that salicylates in large doses prolong prothrombin time<sup>12</sup> and enhance the effect of dicumarol<sup>28</sup> The prothrombin time showed significant rise within 12 hours, but again the crisis proved to be "atypical" and conclusions could not be drawn

The last hemolytic crisis in the series was treated with 400 mg of dicumarol in four divided doses during the first day During the first and second days of the crisis the patient also received 300 mg of heparin in frequent intravenous doses The coagulation time was determined every

\*The whole plasma prothrombin time was prolonged to about double normal and the diluted (12.5 per cent) plasma prothrombin time to between twice and three times normal



simultaneous capillary blockade, initiating a new crisis. By this capillary blockade far greater proportions of sickled red blood cells are destroyed than of those which are still normal in shape. Thus at the end of a crisis there are in circulation relatively few erythrocytes in the sickled form. The abnormal form, however, gradually increases in the circulation during the 10 to 30 days between crises until it reaches a certain critical limit, at which time the massive precipitation of elongated erythrocytes again occurs. The trigger mechanism which sets off this precipitation appears most probably to be a change involving a temporary increase in blood coagulability, and will be discussed presently. During the intercritical period there is by no means a cessation of hemolytic activity. Great numbers of the long brittle erythrocytes are still broken up by the trauma of capillary passage, as reflected in the sustained hyperbilirubinemia. There may also be a small degree of capillary thrombosis contributing to the sustained low-grade hemolysis. There is, however, a relative equilibrium between hemolytic and blood regenerative factors, a condition favorable to the latter, as the level of red elements in the blood rapidly builds up during this relatively quiescent period.

It has been our observation that normoblasts, reticulocytes, and red cells showing polychromatophilia or other evidences of immaturity are very rarely seen in sickled form. Although sickled normoblasts have been reported,<sup>7, 30</sup> it is commonly noted that none of the younger forms of the red blood cell sickle readily.<sup>5, 7, 30, 40</sup> Sickling, therefore, is partly a function of age, at least to the extent that immature erythrocytes are less susceptible to the tendency than are the mature cells. In other words the sickling threshold (as determined by the oxygen concentration of the blood) decreases as the cell ages. Presumably the threshold is first reached under the conditions prevailing in venous blood so that the cell sickles only as it emerges from the venous end of the capillary, and resumes normal shape upon reoxygenation in the lungs. If the decrease in sickling threshold is progressive the change will thereafter occur more and more toward the arterial end of the capillary until finally the threshold passes below the oxygen tension of arterial blood. At this point the cell becomes permanently sickled as long as it remains in the body.

Immediately after the massive destruction of erythrocytes which accompanies a crisis, the circulating blood cells tend to be young, with immature forms constituting a large fraction of the total number. As the red cells mature during the quiescent interval they become increasingly more susceptible to the sickling tendency, with a resulting gradually increasing accumulation of sickled forms between the crises.

This accumulation of sickled forms might be prevented or minimized if the red blood cells were more easily destroyed while in sickled than in normal form. However, no evidence has been advanced to suggest that sickling *per se* shortens the life of the red blood cell. Sydenstricker,<sup>31</sup> using the wet smear technique, recovered sickle cells from a normal subject 23 days after transfusion with the blood of a patient with sickle cell disease, thus proving

their longevity for at least this period. Although it cannot be proved that these cells were all circulating in sickled form, the nature of the sickled cell suggests in any case that it is probably more resistant to the phagocytic action of the reticulo-endothelial system than are normal erythrocytes. The erythrocyte in sickled form has been demonstrated to have a decreased resistance to physical trauma,<sup>5</sup> as might be predicted from its observed rigid and inflexible character. Its resistance to osmotic trauma, on the other hand, is markedly increased over that of normally shaped erythrocytes, as is noted in fragility tests and in our observations that the sickled cell never crenates. Therefore, although the erythrocyte in sickled form is more easily broken up by the trauma of capillary passage, its resistance to chemical and osmotic traumata, which are presumably the destructive weapons of the reticulo-endothelial system, may be abnormally great. Normal erythrocytes lose their resistance to the destructive action of histiocytes as they become old, and when senile are finally phagocytized. The sickled erythrocyte presumably becomes all the more unalterably sickled as it approaches senility, and may thus increase rather than lose its resistance to phagocytosis with age. Such an hypothesis is entirely compatible with the common observation at autopsy that there is a high degree of phagocytosis of sickled cells throughout the reticulo-endothelial system, an observation which has frequently been urged as evidence for the hypothesis that sickled cells are more easily destroyed than normal cells.<sup>1-4</sup> This observation may be used equally well as evidence for our diametrically opposite hypothesis. The erythrocytes seen in the Kupffer cells and other histiocytes may represent whole sickled cells, broken particles of previously traumatized sickled cells, or cells which were ingested while normal in shape and which sickled immediately thereafter. In any of these three cases then prolonged resistance to destruction by the histiocytes which have engulfed them may well explain the high degree of phagocytosis and hemosiderosis which persists and is found at autopsy.

During a hemolytic crisis it is the mature erythrocytes or those that sickle most readily which are chiefly involved in the massive mechanical and thrombotic destruction of red blood cells. The immature forms tend to retain their normal shape. Some of these must become caught in the meshworks of conglutinated sickled cells, but for the most part those red cells which have not sickled will tend to escape hemolysis because they offer no obstruction in capillary passage. As a result the blood literally becomes "rejuvenated" by a crisis. The young red blood cells which thus escape destruction may well become the sickled forms which develop during the next intercritical period and which are in turn responsible for the next crisis.

It might still be argued that the initiation of crises is associated with the development of sudden hypersicklelema. During a crisis great numbers of young red blood cells are thrown into the circulation and there is marked evidence of marrow stimulation. The reticulocyte count rises, large numbers of normoblasts appear, and the leukocyte series may even show a marked myeloblastosis. If it were supposed that sickling occurs at a uniform age

in all of the red blood cells, then there would be a fairly abrupt rise in the rate of sickling at a certain definite interval after the sudden rise in reticulocytosis. However, the evidence does not support such a supposition. Furthermore the initiation of a crisis is so dramatically acute that it could hardly be due to such a gradual process.

The trigger mechanism which sets off the massive precipitation of sickled erythrocytes and blockade of capillaries seems most probably to be an altered state of blood coagulability. As has been discussed, the features most characteristic of the pathologic lesions of sickle cell disease are mechanical obstruction of capillaries and vascular thromboses. These two factors are closely interrelated. Once stasis of blood occurs for whatever cause, thrombosis necessarily supervenes.<sup>24</sup> Furthermore a sudden increase in blood coagulability must in turn enhance the tendency to capillary blockade, as vessels which were only partly occluded thereby become thrombosed. Although a small proportion of the circulating sickled cells is being continually broken up and lysed, the rate of their destruction is apparently not great enough to establish an equilibrium. The result is a progressive reaccumulation of the sickled form in the circulation. Until an equilibrium is reached between the maturing-sickling process on the one hand and the breaking up of the sickled forms on the other, the circulation must progress toward "saturation" with sickled forms, in the sense that any further increase becomes incompatible with free circulation. Then the abnormal erythrocytes will begin to precipitate out into the capillaries at the same rate that they sickle. If it should happen, just at this stage, that an excess of blood coagulants were suddenly thrown into the circulation, the sickleemia would thereby be changed from a "saturated" to a "supersaturated" condition, and precipitation would take place in a massive capillary blockade favored by the increased tendency to capillary thrombosis.

Local thromboses have been found to be reflected in a systemic response in the order of increased coagulability of the blood.<sup>30a</sup> Especially is this true when thrombosis is by coagulation (fibrinous) as opposed to simple agglutination. Our biopsy picture of capillary blockade reveals a fibrin network.

It is shown by clinical and pathological studies that the coagulability of the blood does increase in association with the crises. Thrombosis of large vessels such as the cerebral arteries,<sup>2,3</sup> pulmonary arteries<sup>41</sup> and large abdominal vessels is one of the constant manifestations of sickle cell disease in its active phase. These thromboses are obviously not due to mechanical obstruction, as occurs in blood vessels of very narrow lumen, but reflect, instead, a true thrombotic tendency of the blood. Thromboses of this sort are not reported as occurring during the quiescent phase of the disease.

The mechanism of the rather abrupt change in blood coagulability which accompanies the crises may be explained by a progressive increase in the degree of capillary obstruction associated with the accumulation of sickled cells in the circulation. A thrombus forms in each of the tiny columns of blood as

soon as it becomes static,<sup>24</sup> with the result that small amounts of coagulating substances such as free thrombin and thromboplastin are released into the circulation\*. Under normal circumstances these substances are disposed of and probably cause no increase in total concentration of coagulating substances. However, when the degree of capillary blockade and thrombosis becomes so extensive and generalized that the red cells begin to precipitate into the capillaries as fast as they sickle, the concentration of free coagulants may actually be increased in the blood as a whole. However slight this excess of circulating coagulants may be, it will necessarily encourage the tendency to thrombosis of imperfectly occluded capillaries, with the result that both the coagulability of the blood and the tendency to capillary obstruction and occlusion begin to rise sharply. Once the rate of thrombosis rises the thrombotic tendency of the blood is further accelerated, and the crisis rapidly gathers momentum.

The curve of arterial and venous prothrombin times is of interest in this regard. There is a tendency for the level of prothrombin to become significantly reduced immediately as the crisis becomes clinically perceptible and then to increase about 24 hours after the onset. A clear explanation for these precritical prothrombin time prolongations is lacking, but it is interesting to speculate that they may be the result of excessive utilization coincident to the diffuse thrombosis, the prothrombin elaborating mechanism being unable to respond adequately for about 24 hours when the level commences to approximate normal. On the other hand, it may represent a protective and compensatory mechanism whereby the organism attempts to inhibit coagulation in the face of spreading thrombosis. Similar phenomena have been detected clinically coincidentally with hypercoagulability of the blood in other thrombotic conditions<sup>29, 30</sup>.

#### COMMENT

The ultimate disturbance of sickle cell disease is not to be found in an analysis of its ostensible pathology, but rather in a fundamental abnormality of erythropoiesis. The asymptomatic sickle cell trait was exhibited by the father of the patient here presented. It differs from the clinical disease only in a higher threshold of sickling of the erythrocytes<sup>31</sup>. In both conditions all of the erythrocytes are affected, in that they can all be made to assume the abnormal form<sup>32</sup>.

#### SUMMARY

In sickle cell disease there occur hemolytic crises of varying severity separated by periods of relative quiescence. Accompanying the crises are fever and disseminated pains produced by multiple infarctions which may be visceral as well as skeletal. Hemolytic aspects representing resolution of thrombi and disintegration of the sickled cells are prominent.

\*The hyaline segments disclosed in the electrophoretic pattern, might play an important role in the mechanism.



The pathology of sickle cell disease is determined by the diffuse infarcts, which in turn stem from the abnormal shape and other physical characteristics of the sickled erythrocyte

During the time a susceptible cell retains the normal shape it is indistinguishable in behavior from normal erythrocytes. The act of sickling, however, renders it elongated and rigid, making capillary passage difficult. As the sickled forms gain prominence in the blood stream they eventually form a mechanical impaction delaying the capillary flow. As a result of the static blood flow thrombosis takes place. This constitutes the fundamental pathologic lesion of sickle cell disease.

All erythrocytes of a subject with the asymptomatic sickle cell trait are capable of assuming the abnormal form and differ from those of persons who exhibit the crises only in that they (the former) possess a higher threshold of sickling.

Susceptible red cells exhibit increased tendency to sickling as they mature. Evidence is lacking that sickling affects the longevity of an erythrocyte, hence the abnormal form tends to increase progressively during the quiescent periods until mechanical obstruction and thrombosis of capillaries occur. With each thrombosis there are liberated into the circulation certain coagulating bodies (thrombin, thromboplastin) which further enhance thrombosis and accelerate the precipitation out of the circulation of sickled red cells. A self-perpetuating sickle cell "crisis" is thereby inaugurated which gains momentum until the major part of the sickled cells are destroyed and the blood is again "rejuvenated" by release into the circulation of immature normally shaped cells.

The sudden liberation of coagulating bodies into the circulation accounts for thrombosis of larger blood vessels also.

Anticoagulant therapy appears to be inadequate to prevent a crisis. If in effect at the abrupt onset of a crisis anticoagulants might postpone the thrombotic tendency of the blood, they could not, however, prevent the increased tendency of the cells to sickle as they grow older, which tendency leads inevitably to the vascular occlusions.

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#### BIBLIOGRAPHY

- 1 BAUER, J. Sickle cell disease, *Arch Surg*, 1940, **41**, 1344
- 1a BECK, J. S., and HERTZ, C. S. Standardized sickle cell method and evidence of sickle cell trait, *Am Jr Clin Path*, 1935, **v**, 325
- 2 BRIDGERS, W. H. Cerebral vascular disease accompanying sickle cell anemia, *Am Jr Path*, 1939, **45**, 353
- 3 CONNELL, J. H. Cerebral necrosis in sickle cell disease, *Jr Am Med Assoc*, 1942, **CXLIII**, 893
- 4 CUMMER, C. L., and LAROCO, C. G. Ulcers of the legs in sickle cell anemia, *Arch Dermat and Syph*, 1940, **41**, 1015

5. DIGGS, L W, and BIBB, J The erythrocyte in sickle cell anemia, *Jr Am Med Assoc*, 1939, cxii, 695
6. DIGGS, L W, and CHING, R E Pathology of sickle cell anemia, *South Med Jr*, 1934, xxvii, 839
- 6a. DIGGS, L W, and PETTIT, V D A comparison of the methods used in the detection of the sickle cell trait, *Jr Lab and Clin Med*, 1940, xxv, 1106
7. DIGGS, L W, PULLIAM, H N, and KING, J C The bone changes in sickle cell anemia, *South Med Jr*, 1937, xxx, 249
8. GETZOFF, P L Priapism in sickle cell anemia, *Jr Urol*, 1942, xlviii, 707
9. GRAHAM, S C A case of sickle cell anemia with necropsy, *Arch Int Med*, 1924, xxxiv, 778
10. GRAHAM, S C, and MCCARTY, S H Notes on sickle cell anemia, *Jr Lab and Clin Med*, 1927, xii, 536
11. HAHN, E V, and GILLESPIE, E B Sickle cell anemia Report of a case greatly improved by splenectomy Experimental study of sickle cell formation, *Arch Int Med*, 1927, xxvix, 233
12. HALDANE, J B S Heredity and politics, 1938, W W Norton & Co, N Y
13. HAM, T H Case records of the Massachusetts General Hospital, Case No 27421 (discussion), *New England Jr Med*, 1941, ccxxv, 626
14. HARDEN, A S Sickle cell anemia, changes in the vessels and in the long bones, *Am Jr Dis Child*, 1937, liv, 1045
15. HUCK, J G Sickle cell anemia, *Bull Johns Hopkins Hosp*, 1923, xxxiv, 335
16. KLINEFELTER, H F The heart in sickle cell anemia, *Am Jr Med Sci*, 1942, cciii, 34
17. LINK, K P, OVERMAN, R S, SULLIVAN, W R, HUEBNER, C F, and SCHEEL, L D Studies on the hemorrhagic sweet clover disease XI Hypoprothrombinemia in the rat induced by salicylic acid, *Jr Biol Chem*, 1943, cxlvii, 463
18. MALLORY, T B (ed) Case records of the Massachusetts General Hospital Case No 27421, *New England Jr Med*, 1941, ccxxv, 626
19. MCGAVACK, H, and NUSSBAUM, C C Skin manifestations of sickle cell anemia, *Urol and Cutan Rev*, 1942, xvi, 194
20. MOORE, S Bone changes in sickle cell anemia with note on similar changes observed in skulls of ancient Mayan Indians, *Jr Missouri Med Assoc*, 1929, xxvi, 561
21. MORRISON, M, SAMWICK, A A, and LANDSBERG, E Sickle cell anemia in the white race, *Am Jr Dis Child*, 1942, lxi, 881
22. MURPHY, R C, JR, and SHAPIRO, S Sickle cell disease I A study of the erythrocytes, *Arch Int Med*, 1944, lxxiv, 28
23. OGDEN, M A Sickle cell anemia in the white race, *Arch Int Med*, 1943, lxxi, 164
24. PENNELL, S A platelet-red cell conjugation phenomenon and its relation to blood coagulation, *Am Jr Med Sci*, 1913, ccc, 562
25. SHAPIRO, S Studies in prothrombin V Arterial and venous plasma prothrombin time in man, *Jr Lab and Clin Med*, 1943, xxviii, 1596
26. SHAPIRO, S, REDISH, M H, and CAMPBELL, H A Studies on prothrombin The prothrombinopenic effect of salicylate in man, *Proc Soc Exper Biol and Med*, 1943, lxi, 251
27. SHAPIRO, S, REDISH, M H, and CAMPBELL, H A Studies on prothrombin II The effects of a single small dose of Dicumarol (3,3'-methylenebis(4-hydroxycoumarin)) in liver disease, *Am Jr Med Sci*, 1943, ccv, 803
28. SHAPIRO, S, and SHAPIRO, B Studies in thromboembolization II Observations on the use of Dicumarol (3,3'-methylenebis(4-hydroxycoumarin)) in embolization Report of five cases, *New York State Jr Med*, 1943, xliii, 45
29. SHAPIRO, S, SHAPIRO, B, and CAMPBELL, H P Post-operative thromboembolization The platelet count and the prothrombin time after vaginal operations, *Am Jr Med Sci*, 1942, ccii, 175

- 30 SHAPIRO, S, SHERWIN, B, REDISH, M, and CAMPBELL, H A Prothrombin estimation  
A procedure and clinical interpretations, *Proc. Soc Exper Biol and Med*, 1942, 1, 85
- 30a. SHAPIRO, S Hyperprothrombinemia, a premonitory sign of thrombo-embolization,  
*Jr Exper Med and Surg*, 1944, xi, 2
- 31 SHERMAN, I J The sickling phenomenon with special reference to the differentiation  
of sickle cell anemia from the sickle cell trait, *Bull Johns Hopkins Hosp*, 1940, lxxvii,  
309
- 32 SKOOG, A L Cerebral complications in sickle cell anemia, *South Med Jr*, 1940, xxxiii,  
714
- 33 SNYDER, L H Medical genetics, 1941, Duke Univ Press, Durham, N C
- 34 STANLEY, J Erythrophagocytosis and hemosiderosis in the liver and spleen in sickle cell  
disease, *Am Jr Path*, 1943, xix, 225
- 35 SYDENSTRICKER, V P Further observations on sickle cell anemia, *Jr Am Med Assoc*,  
1924, lxxxiii, 12
- 36 SYDENSTRICKER, V P, MULHERIN, W A, and HOUSEAL, R W Sickle cell anemia, *Am  
Jr Dis Child*, 1923, xxvi, 132.
- 37 VRYONIS, G Studies of the effect of intravenous administration of liver extract in pa-  
tients with sickle cell anemia An unusual response, *Jr Lab and Clin Med*, 1941, xxvi,  
1470
- 38 WADE, L J, and STEVENSON, L D Necrosis of the bone marrow with fat embolism in  
sickle cell anemia, *Am Jr Path*, 1941, xvi, 47
- 39 WALKER, D W, and MURPHY, J P Sickle cell anemia complicated by acute rheumatic  
heart disease and massive cerebral hemorrhage, report of a case, *Jr Pediat*, 1941, xix,  
28
- 40 WERTHAM, F, MITCHELL, N, and ANGRIST, A The brain in sickle cell anemia, *Arch  
Neurol and Psychiat*, 1942, xlvii, 752
- 41 YATER, W M, and HANSMANN, G H Sickle cell anemia, a new cause of cor pul-  
monale, *Am Jr Med Sci*, 1936, cxci, 474
- 42 LONGSWORTH, L G, SHEDLOVSKY, T, and MACINNES, D A Electrophoretic patterns  
of normal and pathological human blood, serum and plasma, *Jr Exper Med.*, 1939,  
lxx, 399.

TABLE II

Beriberi Heart Disease, Incidence of Traditional Signs, Ten Cases at Cincinnati General Hospital, 1940 to 1944

| Name  | Age | Sex | Abnormally Rapid* Circulation | Prominent Rt Heart | "Pistol Shot" | Gallop Rhythm | Syncope or Shock | Critical Improvement After Specific Treatment | Comment          |
|-------|-----|-----|-------------------------------|--------------------|---------------|---------------|------------------|---|------------------|
| H R   | 41  | M   | 40 sec<br>0                   | 0                  | 0             | +             | +                | 0   | Died, autopsy    |
| H S   | 46  | M   | ?                             | 0                  | 0             | 0             | +                | 0   | Died, autopsy    |
| F R   | 33  | M   | 21 sec<br>0                   | +                  | 0             | +             | +                | 0   |                  |
| T. B  | 53  | M   | 14 sec<br>+                   | +                  | 0             | 0             | 0                | 0   |                  |
| J. K. | 47  | M   | 13 sec.<br>+                  | +                  | +             | 0             | 0                | 0   |                  |
| M D   | 56  | F   | ?                             | 0                  | 0             | 0             | 0                | +   |                  |
| J D.  | 55  | M   | 13 sec<br>+                   | 0                  | 0             | 0             | 0                | 0   |                  |
| G B   | 67  | M   | 52 sec<br>0                   | +                  | 0             | +             | +                | 0   | Died, no autopsy |
| J B   | 39  | M   | 13 sec<br>+                   | ?                  | ?             | 0             | +                | 0   | Died, no autopsy |
| J B   | 53  | M   | 11 sec<br>+                   | ?                  | ++            | +             | 0                | 0   | No neuritis      |

\* Decholin method for "circulation time "

follows recovery. Due regard to the possibility of hydrops of the pericardium can usually eliminate pericardial effusion as the sole cause for increased diameters

The term "normal rhythm" as used means a normal origin and propagation of the heart beat, even if gallop rhythm is present

Venous pressures were done directly, and 10 cm of water regarded as the upper limit of normal. It is assumed that in some of our patients in severe shock and with systolic arterial pressures below 100 a venous pressure of 10 cm. may be a high venous pressure

I consider the diagnosis of neuritis the most important point in determining that the patient is deficient in his store of vitamin B<sub>1</sub>, and refer to the article of Dr Aring,<sup>1</sup> Neurologist in the Cincinnati General Hospital, for criteria of diagnosis. When there is much edema, signs of neuritis may be obscured, and they may be demonstrable only after edema subsides. Since neuritis of the lower extremities does not clear rapidly even when treated, it is expected that some residual signs will remain in every case. It is not believed that dependent edema can cause or simulate neuritis

The importance of finding signs of pellagra in a person with heart disease arises from our concept of pellagra as a multiple deficiency. We find many patients who have been diagnosed as pellagrous who later show neuritis also. Therefore, in assessing the state of nutrition as an index of the store of vitamin B<sub>3</sub>, a diagnosis of pellagra is next in importance to the diagnosis of beriberi.

The electrocardiographic changes are always slight and have been mentioned by many cardiologists, viz., "small complexes, negative T-waves in Lead I, and slight aberration of the ventricular complexes" (White).

As to the sixth criterion it is patent that the less one looks for the causes of heart disease the less will be "evident." For that reason it is our custom to defer to the cardiologists whose special technics in recent decades have eliminated as etiologic agents in the causation of heart disease such factors as the use of aspirin, athletic heart, beer drinking, lead, tea, coffee, and perhaps even tobacco.

In estimating gross deficiency of diet we rely on the members of the Department of Dietetics, who, by a method of diet survey, are able to report as "good, fair or poor" the qualities of the recent diet. The minimum duration of such a diet was arbitrarily set at three months. The experimental production of human beriberi by Williams and others<sup>4</sup> has aided in this arbitrary choice.

The specific treatment generally used was 20 to 50 mg. of thiamin intravenously given daily for a space of two weeks. This is known to be an excessive dose, but no harm has come from it. We have usually withheld this specific treatment until the effects of bed rest could be observed. During this period of control and study digitalis and diuretics have occasionally been given. Usually beriberi heart disease is not improved by either, but the result of such treatment is not sufficient to demonstrate the nature of the disease. There is now no certain therapeutic test which will prove the diagnosis of beriberi or exclude it. We regard improvement with reduction of heart size as very suggestive because there are so few diseases of the heart in which prompt and lasting reduction occurs during the ordinary treatment in the hospital. We do not consider the failure to improve with thiamin treatment as proof that beriberi is to be excluded. Our case, H. R., is an example.

As to the diagnosis at autopsy our colleague, Dr. Austin, follows the criteria of the New York Heart Association as published in 1939, viz., "Microscopically the myocardium may show no changes or the myocardial fibers may present various degrees of hydropic degeneration. Longitudinal and cross-striations may remain. Intercellular edema, congestion, hemorrhage and swelling of the connective tissue may be present. These changes, however, are not specific."

The differential diagnosis must exclude Fiedler's myocarditis or isolated myocarditis. In this we follow the criteria as published by Karsner<sup>6</sup>. Separation of beriberi from idiopathic hypertrophy with mural thrombosis and

from congenital idiopathic hypertrophy may be impossible with the present criteria for the clinical recognition of those diseases. A recent discussion of this problem by William Dock<sup>7</sup> and the report by Kugel and Stoloff<sup>8</sup> show the difficulty that develops as nutritional study is added to the usual methods. The essence of that discussion and the report on congenital idiopathic hypertrophy is that both these conditions may be due to deficiency disease.

When the 10 patients at the Cincinnati General Hospital diagnosed by the criteria in table 1 are examined for the traditional signs of beriberi heart disease, the findings are as summarized in table 2. It can be seen that rapid circulation was found in five of eight patients tested by the decholin method. Slow circulation was found three times. In no instance was the time abnormally short, but the time was short in view of the degree and duration of congestive failure when specific treatment was started.

Prominent right heart was described four times by the clinicians who noted abnormal pulsation over the pulmonary conus and accentuation of the pulmonary closure. There was no electrocardiographic, radiographic or necropsy evidence of right ventricle hypertrophy.

"Pistol shot" sound was recorded twice and was not tested once. In both patients a large pulse pressure was found when "pistol shot" was recorded. In one instance loud "pistol shot" was heard in each dorsalis pedis artery (J B in table 2). In all the others the pulse and blood pressure were not suggestive of rapid circulation.

These three traditional signs of accelerated blood flow have been emphasized in the writing of Wenckebach and in his explanation of causes.<sup>9</sup> Porter and Downs<sup>10</sup> applied modern physiologic methods to a study of these three signs in patients at the Brigham Hospital. The latter were unable to conclude that such circulatory faults were important as a cause nor even essential to the diagnosis. Our experience is in harmony with them and not with that of White, who seems to regard "vasodilatation and rapid blood flow as a late sign or occurring only in advanced cases." We have seen this sign in three patients known to be chronic alcoholics at a time when no sign of failure could be shown and who are not, therefore, included in this series. In these three patients rapid heart and rapid blood flow were critically changed by treatment but they did not show heart disease otherwise. One such patient was readmitted eight years later with failure (J D in table 2). One half of our patients showed very low blood pressure or attacks of syncope or both. The high incidence of such signs of danger has made us reluctant to make a prolonged control study for purposes of diagnosis and to explore the nature of the disordered circulation when such signs are present.

When our proposed criteria and the traditional criteria are considered as a whole, it appears that beriberi heart disease is both a myocardial disorder and a disease of the nervous system, and comprises no rigid syndrome. In this we are entirely in harmony with the last published views of Soma Weiss,<sup>11</sup> but we think that undue emphasis on the traditional criteria will

exclude many cases from recognition and treatment. When such case material as can be found in recent literature is tested by these traditional criteria very few cases conform. The case material studied by Jolliffe and Goodhart<sup>12</sup> with regard to the cardiovascular complications of chronic alcoholism also did not show acceleration of the circulation or enlargement of the right heart as a predominating feature or a late sign.

### SUMMARY

We concur in the opinion of the late Soma Weiss that beriberi heart disease is both a disturbance of the myocardium and the nervous system, and that it is not a rigid syndrome nor a rare one. The following criteria are proposed:

Beriberi heart disease may be diagnosed when there is found present

1 Enlarged heart with normal (sino-auricular) rhythm

2 Dependent edema

3 Elevated venous pressure

4 Peripheral neuritis or pellagra

5 Non-specific changes in the electrocardiogram

6 No other cause evident

7 Gross deficiency of diet for three months or more

8 Improvement and reduction of heart size after specific treatment or autopsy findings consistent with beriberi

Rapid peripheral circulation and prominence of the right heart are not often found in the patients recently diagnosed as beriberi heart disease in this country, even though such signs have been regarded as important diagnostic criteria. Suspected and early cases should be subjected to the strict therapeutic control and extensive physiologic study necessary to demonstrate the true nature of the disease. Late cases, especially those showing low blood pressure and syncope, are not suited to such study.

Beriberi heart disease may be found as a complication of other forms of heart disease.

### BIBLIOGRAPHY

- 1 SPIES, T. D., and ARING, CHARLES D. The incidence of neuropathy in pellagra, *Am. Jr. Med. Sci.*, 1940, **CXCIX**, 840-849.
- 2 WEISS, SOMA. The nature of cardiovascular disturbances in nutritional deficiency states (beriberi), *Ann. Int. Med.*, 1937, **XI**, 104.
- 3 WEISS, SOMA. Occidental beriberi: its relation to thiamin therapy, *Jr. Am. Med. Assoc.*, 1940, **CXV**, 832.
- 4 WILLIAMS, R. D., MASON, H. L., and SMITH, B. F. Induced vitamin B<sub>1</sub> deficiency in human subjects, *Proc. Staff Meet. Mayo Clin.*, 1939, **XLV**, 787-793.
- 5 WENCKEBACH, K. F. *Das Beriberi-Herz, Morphologie und Klinik*, Pathogenesis, 1934, Springer, Berlin.
- 6 KARSNER, HOWARD T. Human pathology, 1942, J. B. Lippincott Co., Philadelphia.
- 7 DOCK, W. Cardiac hypertrophy with mural thrombosis, *Arch. Int. Med.*, 1943, **LXXI**, 602.
- 8 KUGEL, M. A., and STOLOFF, E. G. Congenital idiopathic hypertrophy, *Am. Jr. Dis. Child.*, 1933, **XLV**, 828-864.

## MARION A BLANKENHORN

- 9 WENCKEBACH, K F The riddle of the beriberi heart, Libman Anniv Vol, 1932, iii, 1199
- 10 PORTER, R R, and DOWNS, R S . Some physiological observations on circulation during recovery from vitamin B<sub>1</sub> deficiency, Ann Int Med, 1942, xvii, 645-658
- 11 WEISS, SOMA . Nature of cardiovascular disturbances in vitamin deficiency states, Trans Assoc Am Phys, 1936, li, 341-373
- 12 GOODHART, R, and JOLLIFFE, N Rôle of nutritional deficiencies in production of cardiovascular disturbances in alcohol addict, Am Heart Jr, 1938, xv, 569-581



# THE TREATMENT OF BRONCHIECTASIS WITH CHEMOTHERAPY AND ALLERGY MANAGEMENT \*

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THIS study is an evaluation by follow-up examination and questionnaires of sulfonamide therapy and allergy management in the treatment of 75 cases of bronchiectasis. In 13 cases operation was indicated but had been refused or postponed by the patient. The remainder of the cases were considered non-surgical because of minimal or advanced disease, age, general condition, or because benefits from allergy management could be anticipated. The period of observation varied from four months to five years, the majority were observed for two years at least. Consequently, the report is preliminary.

Bronchiectasis was first described by Laennec<sup>1</sup> in 1819, but not until iodized oil as a radio-opaque medium was introduced by Sicard and Forestier<sup>2</sup> in 1922 did the disease become more widely recognized.

Lobectomy has proved to be the only permanently curative procedure. Although improved surgical technic, cutting mortality from 60 per cent prior to 1929 to less than 3 per cent,<sup>3,4,5</sup> has extended radical and curative procedures to less advanced cases, operation is frequently contraindicated because of age, extent of involvement, minimal pathologic lesions, or refusal of operation. For these patients palliative measures have proved of little or no value.

The most obvious feature of bronchiectasis is considered to be inflammation of the tertiary bronchial tubes and adjacent pulmonary parenchyma caused by bacterial infection, which may be secondary to many unrelated conditions of the respiratory tract. That obstruction of a bronchus in addition to bacterial infection is necessary in the production of bronchiectasis has been repeatedly demonstrated experimentally. However, bronchiectasis does not develop from bronchial obstruction in the absence of pulmonary infection. Lisa and Rosenblatt<sup>6</sup> in studying 110 autopsies found that the so-called bronchial dilatation was actually an epithelialized cavity communicating with the bronchus and that these cavities resulted from inflammatory destruction of the bronchial wall. As they pointed out, bronchial obstruction is not a mechanical factor in producing bronchial dilatation, but rather it promotes infection in the bronchus.

Watson and Kibler<sup>7</sup> suggested that primary allergic bronchitis may be an etiologic factor in a large percentage of cases of bronchiectasis. They con-

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tended that allergic swelling of the mucosa and outpouring of tenacious secretions combined with bacterial infection and poor drainage seemed adequate cause for producing atelectasis and, in a variable time, bronchiectasis. Although Watson and Kibler emphasized the importance of atelectasis, the really significant factor seems to be promotion of infection by obstruction and atelectasis and by impairment of function of smaller bronchi and bronchioles such as occurs in bronchial asthma and perennial allergic bronchitis. Although the cough reflex is initiated by exudate or foreign material in the larger bronchi, the smaller branches of the bronchial tree depend upon the action of cilia and musculature for expulsion of foreign material. The impairment of this process in bronchial asthma and allergic bronchitis increases susceptibility to pulmonary infection. Undiagnosed bronchostenosis as a sequel to pneumonia, bronchitis, whooping cough, influenza, or bronchial asthma may be an etiologic factor in the production of bronchiectasis more frequently than is realized. Perennial allergic bronchitis and bronchial asthma are nearly always accompanied by perennial allergic rhinitis which frequently predisposes to sinus infection. There is some disagreement about sinusitis as an etiologic factor in bronchiectasis. However, chronic drainage of septic material from the sinuses may lead to development of bronchiectasis, particularly in persons having bronchial asthma or allergic bronchitis with obstruction and impaired function of the smaller bronchi and bronchioles. Moreover, bacterial sensitivity no doubt plays a large rôle in the relation of allergy and bronchiectasis.

Of 190 consecutive cases of bronchiectasis seen over a five year period 48 per cent had a major allergy of the respiratory tract. In comparison in 15 of the 75 cases in this series the only predisposing factor was allergy of the respiratory tract. In about half of the group with a history of respiratory infection allergy was considered to be a complicating factor. Frequently the symptoms for a number of years after the initial infection were obviously those of allergic bronchitis or sometimes bronchial asthma. In 31 cases sinusitis was found on the initial examination, or there was a history of pus having been found on irrigation of the sinuses, 28 of these had associated allergy of the respiratory tract.

Therefore, since bacterial infection is the fundamental factor in the pathogenesis and symptomatology of bronchiectasis and since allergy is an associated or predisposing factor in such a large percentage of cases, the most logical palliative treatment would include sulfonamide drugs and allergy management. In the future less toxic and more potent drugs will probably replace the sulfonamides. Penicillin should be considered in this group of newer drugs and used in the treatment of bronchiectasis.

Little appears in the literature concerning sulfonamide drugs or allergy management in the treatment of bronchiectasis. Watson and Kibler<sup>7</sup> were the first to point out an allergic factor in the etiology and to suggest allergy management in the prevention and treatment. In 1941 Van Ordstrand<sup>8</sup> suggested the use of sulfonamides. Recently Norris<sup>9</sup> published results in 10

cases in which intratracheal and intrabronchial instillations of 5 per cent aqueous suspension of sulfathiazole combined with bronchoscopy resulted in definite reduction in daily sputum. It was found that the concentration of sulfadiazine in bronchial secretions during oral administration was approximately 60 per cent of the blood level and was not materially affected by the extent of bronchial disease or the amount of expectoration. Harris<sup>10</sup> also used intrabronchial insufflations of sulfathiazole in a few cases with good results. Albritten and Flick<sup>11</sup> used sulfanilamide in partial and total resections of the lung and believed that the incidence of pleural infection was less than when sulfanilamide was not used preliminary to operation. Graham,<sup>12</sup> however, in a series of 23 cases and controls did not find sulfonamides of any help.

### MATERIAL OF STUDY

Thirty of the 75 patients were men and 45 were women. When they first presented themselves for treatment, their ages ranged from 4 to 76. The majority were over 30 years of age (table 1). The age at the onset of symptoms varied from infancy to 69 years (table 2).

TABLE I  
Age When Patient First Presented Himself for Treatment

| Age   | Patients | Per Cent |
|-------|----------|----------|
| 0-9   | 3        | 4        |
| 10-19 | 8        | 11       |
| 20-29 | 8        | 11       |
| 30-39 | 20       | 27       |
| 40-49 | 20       | 27       |
| 50-59 | 11       | 14       |
| 60-69 | 4        | 5        |
| 70-79 | 1        | 1        |

TABLE II  
Age at Onset

| Age   | Patients | Per Cent |
|-------|----------|----------|
| 0-9   | 28       | 37.33    |
| 10-19 | 6        | 9.0      |
| 20-29 | 12       | 16.0     |
| 30-39 | 11       | 14.23    |
| 40-49 | 12       | 16.0     |
| 50-59 | 4        | 5.33     |
| 60-69 | 2        | 2.66     |

The duration of symptoms ranged from two months to 45 years. Fifty-five per cent had symptoms for 10 or more years (table 3).

TABLE III  
Duration of Symptoms

| Duration in Years | Number of Patients |
|-------------------|--------------------|
| Less than 1 yr    | 6 (8%)             |
| 1-4               | 18 (24%)           |
| 5-9               | 10 (13%)           |
| 10-19             | 20 (27%)           |
| 20-45             | 21 (28%)           |

The disease varied in severity from minimal to far advanced. All 75 patients gave a history of cough with expectoration, which was purulent in all but two cases. The amount of expectoration each 24 hours varied from  $\frac{1}{2}$  ounce to 32 ounces. Fifty-five patients expectorated more than two ounces each 24 hours. There was history of frank hemoptysis in 16. Three patients had cor pulmonale. When first seen 26 had fever, usually low grade. Thirty had dyspnea, and 17 had lost weight.

On initial examination of the chest 67 patients had findings typical of bronchiectasis. Stereoscopic roentgenograms of the chest were highly suggestive of bronchiectasis in 35; in 40 they were questionable or negative. Lipiodol bronchography established the diagnosis in 55 cases. Bronchoscopy was done in nearly all of these to rule out any obstructive lesion, in three cases in which the bronchograms were negative or not satisfactory localization was determined by detecting the orifice from which the exudate originated. The diagnosis was established in the remainder of the cases by the history, physical examination, absence of tubercle bacilli and fungi in the sputum, and stereoscopic and plain films of the chest.

TABLE IV

Localization of Pathologic Process in 57 Cases Determined by Bronchograms or Bronchoscopy

|  |    |
|--|----|
| Unilateral                                     | 31 |
| Right, upper lobe                              | 1  |
| Right middle lobe                              | 2  |
| Right lower lobe                               | 10 |
| Left upper lobe                                | 0  |
| Left lower lobe or left lower lobe and lingula | 17 |
| Left upper lobe and left lower lobe            | 1  |
| Bilateral                                      | 26 |
| Lower lobes                                    | 22 |
| Lower and middle lobes                         | 4  |

TABLE V

Type of Bronchial Dilatation

|                       |    |
|-----------------------|----|
| Fusiform              | 31 |
| Saccular              | 17 |
| Fusiform and saccular | 6  |

Bacteriologic studies of bronchoscopic aspirations in 41 patients revealed in order of frequency nonhemolytic streptococcus, *Streptococcus viridans*, hemolytic streptococcus, pneumococcus, fusiform bacillus and spirochetes, fusiform bacillus and streptococcus, *Neisseria catarrhalis*, streptococcus, and *Staphylococcus albus*, and *Haemophilus influenzae*. Nonhemolytic streptococci, *Streptococcus viridans*, and hemolytic streptococcus were found in about one half the cases. Approximately one fourth of the entire group showed pneumococci.

*Etiology.* Table 6 shows the distribution of cases according to predisposing disease and complication of allergy and sinusitis. Fifty-five of the total 75 patients had an associated major respiratory allergy including bronchial asthma, perennial allergic bronchitis, and severe perennial allergic

TABLE VI

## Summary of Treatment

Twenty-Three Cases Treated with Sulfonamides per se, 21 Patients Treated by Allergy Management per se, and 31 Patients Treated on a Combined Management of Allergy and the Use of Sulfonamide Drugs

| Treatment  | Period of Observation | Total Treated | Improvement   |          |        |          | No Improvement                                      | Died           |
|--|-----------------------|---------------|---|----------|--------|----------|---|----------------|
|  |                       |               | Total   | Complete | Marked | Moderate |   |                |
| Sulfonamide drugs                                  | 4 Months to 4 Years   | 23            | 22  | 7        | 12     | 3        | 1   |                |
|  |                       |               | 17 Required more than 1 course of sulfonamide<br>6 Showed improvement after 1 course of sulfonamides for periods from 1-2½ years (except 1 observed for 4 months)<br>11 Had no exacerbations and continued to improve during entire period of observation<br>1 Had other therapeutic measures, i.e. postural drainage |          |        |          | Symptoms not controlled with 3 courses of treatment |                |
| Allergy management                                 | 1 Year to 4½ Years    | 21            | 15  | 4        | 5      | 6        | 5   | 1 <sup>a</sup> |
|  |                       |               | 8 Showed continued improvement of cough for 1-4 years<br>7 Had recurrence of symptoms<br>3 Recurrences associated with discontinuance of hyposensitization program  |          |        |          |   | Cause unknown  |
| Sulfonamide drugs combined with allergy management | 6 Months to 5 Years   | 31            | 26  | 5        | 14     | 7        | 5   |                |
|  |                       |               | 10 Showed no exacerbation<br>16 Reported recurrences of symptoms<br>Recurrences occurred with discontinuation of allergy program and too wide intervals between sulfonamide courses<br>10 Had continued improvement for as long as 4½ years   |          |        |          |   |                |

rhinitis. However, of a total of 190 consecutive cases of bronchiectasis seen at the Clinic over a five year period 92 had major respiratory allergy of sufficient severity to require medical consultation.

The cases following whooping cough or measles were probably complicated by an undiagnosed bronchopneumonia.

An interesting relationship between sinusitis and allergy was noted in this study. Of 30 cases having definite recurrent or chronic sinusitis, all but two had an accompanying major respiratory allergy consisting of allergic bronchitis or bronchial asthma or both almost always accompanied by

perennial allergic rhinitis Six had severe perennial allergic rhinitis without other respiratory allergy

### TREATMENT

Palliative treatment was used to reduce pulmonary infection to a minimum and to eradicate any cause of bronchial obstruction in order to produce an asymptomatic phase without cough, expectoration, hemoptysis, or toxicity Sulfonamide drugs and allergy management were the chief therapeutic measures used

In general the treatment used was as follows:

1. Sulfonamide drugs only were used in 23 cases, of whom 19 were non-allergic individuals and four had moderately severe allergies consisting of perennial allergic rhinitis in three and perennial allergic bronchitis in one Sulfathiazole or sulfadiazine was used in most instances, in a few cases sulfanilamide or sulfapyridine was used The average "course" consisted of 77 grains of the drug four times daily for four weeks The courses were repeated from 0 to 9 times, usually at intervals not less than every three or four months In one case direct intrabronchial instillation of sulfathiazole was done with remarkably good results

- 2 Allergy management only was used in 21 cases in which a respiratory allergy was suspected of being an etiologic or complicating factor in the production of symptoms After thorough allergy investigation the therapeutic program consisted of avoidance of the important offending allergens in the patient's environment, dietary restrictions, hyposensitization with extracts containing the major exciting allergens, and autogenous vaccine incorporated in the hyposensitization program where significant sensitivity was manifested by intradermal reactions These measures were followed for periods varying from four months to three and one-half years

3. In the third group of 31 patients a combined treatment of sulfonamide drugs and allergy management constituted the chief therapeutic measures

Postural drainage was used in 59 patients; 11, however, discontinued it after a short time because they did not find it beneficial The patients were instructed to invert the chest completely for 10 or 20 minutes two or three times daily Some were advised to have the foot of their bed raised during the night Expectorants were prescribed for use prior to postural drainage exercises to aid in the drainage of tenacious sputum For purposes of comparison postural drainage was not advised in 16 cases regardless of the amount of expectoration

Treatment of sinusitis and oral sepsis were instituted to eradicate possible foci of infection whenever it was indicated

General supportive measures such as rest, adequate diet, and vitamins were used as indicated to improve general health

In one case roentgen-ray treatment had been used without benefit

In several of the 12 patients having fusiform bacilli and spirochetes in their sputum, neoarsphenamine had been used without apparent benefit

whole the best results seemed to occur when the two were used simultaneously. It was found that in some cases greater improvement occurred after allergy management had been instituted than had been experienced with the use of sulfonamide drugs alone. On the other hand allergy management frequently gave poor or only fair results until sulfonamide drugs were also used. Whether or not sulfonamide drugs needed to be used in addition to allergy management seemed to depend upon the general health of the patient and upon the severity of his symptoms, however, this was not always true.

Another logical form of treatment to prevent stagnation of bacteria laden secretions is postural drainage exercises. In the majority of cases it was believed to be of definite help in producing temporary symptomatic relief. In the 16 patients who did not do postural drainage exercises at all, there seemed to be no apparent difference in the good results regardless of the amount of expectoration. The same appeared to be true of those who discontinued it of their own accord after only short periods of trial because they did not find it helpful. Others served as their own control in this variable, since they had carried out vigorous postural drainage exercises for a sufficiently long time to obtain maximum relief from this procedure before allergy or sulfonamide treatment was instituted.

No control series is included in this study, it is well known that the disease is chronic and characterized by frequent exacerbations. It was believed that no series of cases would be strictly comparable with one which included so many variables. Since at least 75 per cent had symptoms of bronchiectasis from five to forty-five years they were their own best controls. In making comparisons before and after treatment an attempt was made to determine the average amount of cough and expectoration that had been experienced between exacerbations to see if by controlling complications and by treating the pulmonary infection directly with chemotherapy, there would be improvement of the chronic symptoms as well as reduction in the number of exacerbations.

It may be concluded that the results of this study indicate that all cases having symptoms of bronchiectasis which are nonsurgical should, unless otherwise indicated, be given adequate trial on sulfonamide therapy and that those in which a complicating or etiologic factor is an allergy of the respiratory tract should be placed on allergy management. In the majority of cases improvement entailing at least 50 per cent reduction in cough and expectoration occurred. Exacerbations were frequent in all groups but almost invariably if sulfonamide drugs were repeated when symptoms first began to return to their former severity, continued improvement could be maintained. Likewise, exacerbations occurred often when the allergy program was discontinued.

#### SUMMARY

1. Of 190 consecutive cases of bronchiectasis it was found that approximately one-half had major allergy of the respiratory tract. A clinical study

was made of 75 selected cases of bronchiectasis to evaluate sulfonamide therapy and allergy management in treatment. In 55 of these cases an allergy of the respiratory tract was an etiologic or complicating factor.

2 Twenty-three cases received sulfonamide drugs as the chief or only therapeutic measure and were observed for four months to four years. Twenty-two of these patients showed definite improvement with reduction of cough and expectoration.

3 Twenty-one cases treated chiefly or wholly with allergy management were observed for a period of time ranging from one to four and one-half years. Fifteen of this group showed frank improvement with reduction in cough and expectoration.

4 In 31 cases combined allergy and sulfonamide therapy was used. Twenty-six cases were found to have at least 25 to 100 per cent improvement in cough and expectoration. They were observed for six months to five years.

5 Recurrences of symptoms of original severity were frequently noted following acute respiratory infection, cessation of allergy management, or in some cases when infrequent courses of sulfonamide drugs were used.

#### BIBLIOGRAPHY

- 1 LAENNEC, R. T. H. A treatise on the diseases of the chest and on mediate auscultation. Translated by John Oakes. 4th ed., 1834, T. and A. Underwood, London, pp. 100-108.
- 2 SICARD, J. A., and FORESTIER, J. Methode générale d'exploration radiologique, par l'huile iodee, Bull. et mem. Soc. méd. d'hôp. de Par., 1922, *lvi*, 463-469.
- 3 GRAHAM, E. A., SINGER, J. J., and BALLON, H. C. Surgical diseases of the chest, 1935, Lea and Febiger, Philadelphia.
- 4 DALLEY, O. S., and JONES, J. C. Lobectomy and pneumonectomy for lung suppuration and malignancy, Jr. Lancet, 1939, *lix*, 162-168, 268-278.
- 5 OCHSNER, A., and DEBAKEY, M. Surgical considerations of bronchiectasis, Tri-State Med. Jr., 1942, *xi*, 2793-2798.
- 6 LISA, J., and ROSENBLATT, M. B. Bronchiectasis, 1943, Oxford University Press, New York.
- 7 WATSON, S., and KIBLER, C. Bronchiectasis, Jr. Am. Med. Assoc., 1938, *cxi*, 394-395.
- 8 STAFF OF CLEVELAND CLINIC. Allergy in clinical practice, 1941, J. B. Lippincott Company, Philadelphia, pp. 93-111.
- 9 NORRIS, C. M. Sulfonamides in bronchial secretions, Jr. Am. Med. Assoc., 1943, *cxxiii*, 667-670.
- 10 HARRIS, H. Personal Communication.
- 11 ALBRITTEN, F. F., JR., FLICK, J. B., and GIBBON, J. H. The use of sulfanilamide in partial and total resection of the lung, Jr. Thoracic Surg., 1941, *vi*, 187-197.
- 12 GRAHAM, E. A. Discussion of The use of sulfanilamide in partial and total resection of the lung, Jr. Thoracic Surg., 1941, *vi*, 195-196.



# CASE REPORTS

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## STREPTOBACILLUS MONILIFORMIS AS A CAUSE OF SUB-ACUTE BACTERIAL ENDOCARDITIS: REPORT OF A CASE TREATED WITH PENICILLIN \*

By WALSH McDERMOTT, M M LEASK, and M BENOIT, *New York, N Y*

HUMAN infections with the *Streptobacillus moniliformis* have occurred either following a rat bite,<sup>1</sup> or as epidemics of so-called Haverhill fever, presumably due to infected milk.<sup>2</sup> Regardless of source, the clinical picture resulting from infections with this organism is one of an acute infection with abrupt onset, and characterized by chills, relapsing fever, generalized rash and involvement of joints.<sup>3</sup> In the epidemic form, which is generally milder, there have been no deaths, and hence no autopsy material for study has been available.<sup>4</sup> Deaths have occurred from the infection acquired through rat-bite, and a few post-mortem examinations are available.<sup>1, 4, 5, 6</sup> The findings, in general, have been similar to those present in other acute bacterial infections, but in two instances acute ulcerative endocarditis has been described.<sup>1, 5</sup> In contrast to those types of infection, Stuart-Harris and associates in 1935<sup>7</sup> reported a case of streptobacillus infection in an 18 year old boy with previous rheumatic heart disease, in which the presenting picture was that of subacute bacterial endocarditis. We have recently encountered a similar case which constitutes the basis for this report.

*Reports of Cardiac Involvement Following Rat-Bite* In 1916, Blake<sup>1</sup> made the first report of the postmortem findings of a case of *Streptobacillus moniliformis* infection following rat-bite. The patient was a 67 year old woman who died after a two week febrile illness. She had had no symptoms of heart disease, and no cardiac abnormalities were present on physical examination other than a soft systolic apical murmur. There were no embolic phenomena, but shortly before death the murmur became louder and harsher. The *Streptobacillus moniliformis* (known at the time as the *Streptothrix muris rattus*) was isolated from the blood during life. At postmortem examination, the heart weighed 360 gm and the musculature was normal on gross examination. On the posterior cusp of the mitral valve, there was a large (15 by 7 mm) vegetation which had ulcerated through the valve leaflet. On microscopic examination, "masses of organisms appearing as long slender bacilli" were demonstrable in necrotic areas of the vegetation. The aortic, pulmonic and tricuspid valves were normal. Infarcts of spleen and kidney were present. In addition to the endocarditis, a subacute myocarditis with microscopic areas of focal necrosis was present. Re-

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The sodium salt of penicillin used in the treatment of this patient was obtained from Dr Chester S Keefer, Chairman of the Committee on Chemotherapeutics and Other Agents, of the National Research Council

cently, with Horstmann and Arnold, Blake<sup>4</sup> has reported another fatal case of *Streptobacillus moniliformis* infection following rat-bite, in which the important histological finding was this focal myocarditis. No endocarditis was present.

In 1941, Rountree and Rohan<sup>5</sup> reported a fatal infection with *Streptobacillus moniliformis* in a 14 year old girl following contact with a rat. Although a cardiac murmur had been noted at the age of six, there had been no symptoms of heart disease, nor was any evidence of antecedent cardiac disease noted at autopsy. In addition to the relapsing fever, rash, and joint pains characteristic of this infection, endocarditis was evident from the presence of a loud apical

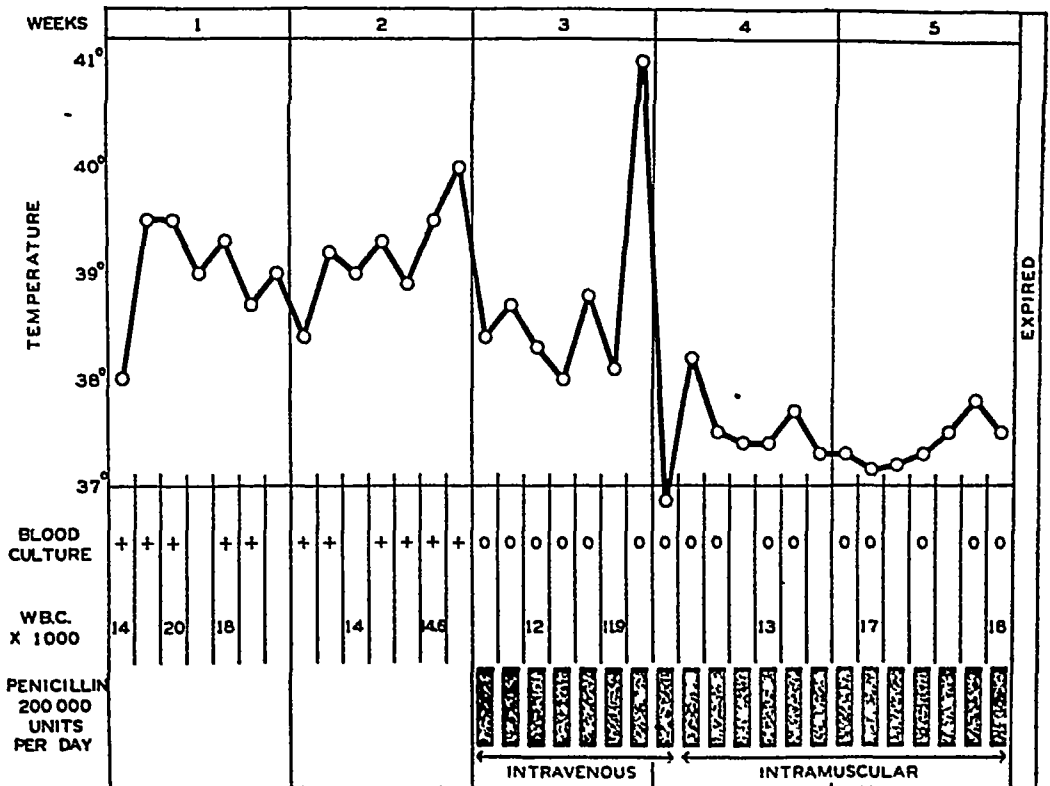


FIG 1 Clinical course of patient with subacute bacterial endocarditis caused by *Streptobacillus moniliformis*

systolic murmur, subungual hemorrhages, and signs of an arterial embolus in the right leg. At postmortem examination, the only cardiac abnormality was a large (30 cm) vegetation on the mitral valve which "had ulcerated through the cusp onto the upper part of the ventricular wall." The spleen was greatly enlarged and contained numerous infarcts. Although two antemortem blood cultures were sterile, the *Streptobacillus moniliformis* was isolated in pure culture from the vegetation on the heart valve.

In a footnote in their comprehensive review of rat-bite fever, Brown and Nunemaker<sup>3</sup> state that unpublished autopsy reports of two fatal cases of *Streptobacillus moniliformis* infection have been brought to their attention. In one, a myocardial abscess was present. Since the other is described as "a patient who

TABLE I

| Media  | Penicillin Concentration in Oxford Units |     |     |     |      |         |       |
|--|--|-----|-----|-----|------|---------|-------|
|  | 10                                       | 0.1 | 0.5 | 0.1 | 0.01 | Control | Hours |
| 4% serum broth   | 0  | 0   | —   | 0   | —    | 3+      | 24    |
|  | 0  | 0   | —   | 2+  | —    | 4+      | 48    |
|  | 0  | 0   | —   | 4+  | —    | 4+      | 72    |
| Thioglycolate<br>5% serum  | —  | 0   | 0   | ±   | 2+   | 2+      | 24    |
|  | —  | 0   | 0   | ±   | 2+   | 2+      | 48    |
|  | —  | 0   | 0   | 1+  | 4+   | 3+      | 96    |
| Blood agar plates in-<br>cubated under 10%<br>CO <sub>2</sub> for 38 hours |  |     |     |     |      |         | 24    |
|  | 0  | 0   |     |     |      | 3+      | 48    |
|  | 0  | 0   |     | ±   | 2+   | 3+      | 72    |
| % blood broth incu-<br>bated under 10%<br>CO <sub>2</sub> for 38 hours     |  |     |     |     |      |         | 24    |
|  | 0  | 0   |     | ±   | 1+   | 2+      | 48    |
|  | 0  | 0   |     | ±*  | 1+†  | 2+      | 72    |

Growth recorded 1 + to 4 +

\* Subculture on serum enriched thioglycolate negative

† Subculture positive

had had endocarditis," it probably resembles the clinical type of subacute bacterial endocarditis reported by Stuart-Harris and the present authors

*Subacute Bacterial Endocarditis* The only published report of this type of streptobacillus infection is in the paper of Stuart-Harris and his associates. Unfortunately, as the emphasis in their report was on the bacteriology of various unusual organisms isolated from patients with endocarditis, the clinical and pathological findings of the patient with streptobacillus infection are merely summarized in one paragraph.

"Walter Gooding, aged 18, was admitted to Hackney Hospital on 27th October 1934, suffering from subacute bacterial endocarditis. He died on 25th November 1934 and the post-mortem findings were typical of this condition supervening on chronic rheumatic endocarditis. An organism, which is of interest in view of its extreme pleomorphism, was isolated aerobically on three occasions during life by blood culture, and appeared in direct films and cultures from the aortic and mitral valves at autopsy. The patient's blood count showed a considerable degree of anemia of the secondary type, accompanied by a moderate polymorphonuclear leucocytosis."

From the detailed description of the bacteriology of this organism, there can be little doubt that it was the *Streptobacillus moniliformis*.

#### CASE REPORT

P. W., a 43 year old supervisor of male nurses, was admitted to the medical service of the New York Hospital on March 4, 1944.

*Chief Complaint* Fever and weakness of two months' duration

*Past History* The patient had had no significant illnesses other than two attacks of rheumatic fever at the ages of 16 and 30. Both attacks were similar and consisted of the development of swollen, painful, red, hot and tender knee and finger joints associated with fever. Following the first attack, which had occurred in Ireland, he was told that he had a heart murmur, but at no time prior to his present illness had he had any symptoms suggestive of heart disease or had he modified his activity in any way.

*Present Illness* In October 1943 (four months prior to admission to New York Hospital) the patient's wife first noticed that he seemed fatigued and had developed a hacking non-productive cough associated with night sweats. In December 1943, the patient first noticed that he was very tired each day after work, was having frequent copious night sweats, and would have minimal swelling of the ankles only in the evening and unassociated with any cardiac symptoms. He stopped work in January 1944 because of easy fatigability, fever, headache, and stiffness of knee and ankle joints. During January and February the intermittent fever continued (maximum of  $40.4^{\circ}\text{C}$ ) and he experienced migratory pains in the knees, toes and fingers with no objective evidence of involvement of the joints. The onset of these pains would be sudden and acute, gradually diminishing over a 24 to 48 hour period. With these episodes of pain, his temperature would increase to a higher level, and on one occasion the tip of the first left finger was swollen and tender for 48 hours.

During the two week period before admission, he had had an episode of sudden severe pain in the left upper quadrant which had gradually disappeared over five days, and a 24 hour period during which he had had difficulty in "pronouncing words."

Although with the fever he had noticed cardiac palpitation, he had had no dyspnea, orthopnea or substernal pain. During a four day period which ended one week before admission, the patient received 100 gm of sulfathiazole and 170 gm of sulfadiazine without any noticeable effect upon his symptoms. The only skin abnormality noted during the entire illness was a transient macular rash over the right buttock and calf which was associated with, and apparently due to the administration of, sulfathiazole.

*Contact with Rats* The patient was employed in a State Hospital, housed in old buildings which contained rats. Two years before his present illness, armed with a broomstick, he had killed a large brown rat in one of the buildings. He stated that he had not handled the animal or the contaminated end of the broomstick, and that since that time to his knowledge he had had no contact with rats whatsoever.

*Physical Examination* The patient was a thin, sallow, well-developed middle-aged white male who appeared to be chronically ill but in no distress. The respirations were rapid but he did not appear to be dyspneic. There was no orthopnea or cough. Temperature was  $38^{\circ}\text{C}$ , pulse rate, 112, respiratory rate, 28. Blood pressure was 140 mm Hg systolic and 40 mm diastolic.

There were no petechiae on the mucous membranes or on the skin, which was pale and sallow. On the lateral aspect of the right calf and over the right buttock there were a few 1 to 2 mm discrete faded pink papules, some of which were excoriated.

The eyes, ears, nose, mouth and throat were negative. The veins in the neck were not distended. Accentuated systolic arterial pulsations were present. There was no enlargement of the superficial lymph nodes.

The chest was resonant, and the breath sounds were vesicular. A few distant fine râles were heard at the left base.

The cardiac impulse was visible over the fourth and fifth interspaces on the left. The heart was enlarged, the left border of dullness extended to the anterior axillary line in the fifth interspace. The sounds were regular in force and rhythm. At the apex, presystolic and systolic thrills were palpable and a rumbling presystolic murmur which ended in a high pitched blowing systolic murmur was heard. Over the aortic

area and down the left sternal border, somewhat lower pitched blowing systolic and diastolic murmurs were present. There were no thrills over the aortic area. The peripheral signs associated with aortic insufficiency were present.

The abdomen was flat, neither the liver nor the spleen was felt. There was marked clubbing of the fingers.

The only abnormalities noted on neurological examination were a slight weakness of the left corner of the mouth, and an extensor plantar response of the left great toe when the sole of the foot was stroked.

**Laboratory Examinations** Blood Hemoglobin was 95 gm, red blood corpuscles 2,900,000 per cu mm, white blood corpuscles 14,000 per cu mm, neutrophils 75 per cent (nonsegmented forms 20 per cent), lymphocytes 20 per cent, large mononuclears 2 per cent, eosinophiles 1 per cent.

**Urine** Yellow, clear, acid, specific gravity 1.012, albumin 0, sugar 0, sediment occasional white blood corpuscle.

**Blood Cultures** *Streptobacillus moniliformis* was recovered in pure culture on 11 separate occasions between March 4 and March 16 inclusive. Sixteen blood cultures taken from March 17 to April 7 inclusive were sterile (during penicillin therapy).

**Roentgen-ray** Examination of the chest on March 4, 1944, showed marked cardiac enlargement with an enlarged left auricle and prominent pulmonary markings due to congestion.

**Electrocardiogram** On admission, before digitalization, there was beginning deviation of the electrical axis to the right and minimal splitting of the QRS complexes. Electrocardiograms taken after digitalization and as the disease progressed showed evidences of overdigitalization and progressive myocardial damage.

**Course of Illness** During the first two weeks in the hospital, the patient's fever continued with daily elevations to 39.4° C, and embolization of the tips of several fingers and toes occurred. When it was established that penicillin inhibited the streptobacillus in vitro, therapy with this agent was started on the fourteenth hospital day. He received 200,000 Oxford units daily for a period of 21 days. The material was administered by continuous intravenous drip for the first eight days, and by the intramuscular route for the succeeding two weeks. No heparin was used.

During the first week of therapy, the patient's fever started downward, and during the second and third weeks his temperature was only rarely above normal. With the exception of one conjunctival petechia which appeared the day after penicillin was started, no definite evidence of further embolization appeared. All 16 blood cultures taken after the institution of therapy were sterile. However, despite the marked improvement in the signs of the infection, the patient gradually developed cardiac failure which was steadily progressive and resulted in death on April 9.

**Clinical Diagnosis** Rheumatic heart disease with stenosis and insufficiency of mitral and aortic valves, subacute bacterial endocarditis (*Streptobacillus moniliformis*).

**Autopsy Protocol** Autopsy was performed six hours post mortem. There were no abnormalities of the skin, eyes, ears, nose, throat or superficial lymph nodes. There were no adhesions or free fluid in the abdominal cavity. There were 1,100 cc of fluid in the right pleural cavity and 900 cc in the left pleural cavity. There were 75 cc of fluid in the pericardial cavity. The parietal pericardium was gray-white, smooth and glistening.

The heart weighed 600 grams. The epicardium was glistening, transparent, and contained a moderate amount of fat in the coronary sulci. The right ventricular wall measured 5 mm in thickness. The left ventricular wall measured 14 mm in thickness. The myocardium was red and soft. No infarcted areas were seen. The myocardium of the left ventricle was split, and appeared red with some small yellow

areas The tricuspid valve measured 14 cm in circumference, pulmonic 9 cm, mitral 12.5 cm, and aortic 8.5 cm The tricuspid and pulmonic valve leaflets appeared thickened and stretched On the mitral valve cusp edges there were collections of irregular, crumbly, friable material which was fairly adherent The chordae tendineae were not thickened or shortened In fact, many of them were stretched, and some had ruptured Some of them were also encrusted with vegetations The endocardium of the left auricle above the posterior leaf of the mitral valve appeared slightly thickened, but no vegetations were present The aortic valve at first glance had the appearance of a bicuspid valve This was because two of the commissures of the cusps had been destroyed, so that there was practically a total obliteration of the space between two of the cusps The valve leaflets were also thickened and encrusted with more of the vegetations The left circumflex coronary artery had its origin adjacent to that of the right coronary artery

*Microscopic Examination* Section of the myocardium in the left ventricle showed the myofibrils to be hypertrophied and fragmented in many areas Fibrous tissue deposition was widespread There were many focal accumulations of lymphocytes around vessels, especially in the fibrotic areas

A section of myocardium stained with Sudan III showed a marked deposition of fat in the myofibrils underneath the ventricular endocardium

Examination of the other organs disclosed infarcts of the spleen and left kidney, slight arteriosclerosis of the aorta, and the characteristic changes of chronic passive congestion in the lungs

*Bacteriology* The initial blood culture (March 4) in standard beef-heart-infusion broth showed no growth In a second culture (March 5) in this same medium, tiny white granular "balls" appeared, resting on the undisturbed sedimented blood cells after five days of incubation Gram stains of these colonies, picked up with a long slender capillary pipette, showed short chains looped about the blood cells These were at first mistaken for cocci, but, on further observations, gram-variable streptobacilli, diphtheroid and other pleomorphic forms were seen All 11 blood cultures on this medium taken prior to penicillin therapy presented the same findings

Subcultures of this "ball" growth were made in duplicate on various media, one set enriched with blood or serum, the other without enrichment The serophilic nature of the organism was evident when good growth and marked pleomorphism occurred in the enriched media whereas all subcultures on unenriched media were uniformly sterile Incubation with 10 per cent CO<sub>2</sub> improved growth somewhat, but was not essential Transplants were made daily to ensure viable cultures Loeffler's serum and dextrose-starch-serum-agar were selected for subsequent cultures The former proved highly satisfactory for the development of the large disc-like forms referred to by Klieneberger as 'L' forms The dextrose-starch-serum agar supported growth, not only of the larger, but also of the pinpoint colonies designated as "L-1" All of the classical forms of the *Streptobacillus moniliformis* described originally by Schottmüller<sup>8</sup> and Blake<sup>1</sup> and the forms subsequently described by Klieneberger<sup>9</sup> developed on these two media The characteristic marked pleomorphism was shown by the presence of long and short filaments with terminal and sub-terminal swellings sometimes projecting from one side only, fragmented forms with the appearance of streptococci, a variety of diphtheroid club-shaped and coccobacillary forms and an occasional "snake-like" form

*Postmortem Cultures* Blood cultures taken from the heart showed no growth Cultures from vegetations of mitral and aortic valves were unfortunately so heavily overgrown with *E. coli* and other postmortem invaders that repeated attempts to isolate *Streptobacillus moniliformis* proved unsuccessful

Numerous typical forms, however, were seen in stained contact films as also in stained preparations from suspensions of ground-up tissue from these valves sug-

gesting that these organisms were still present, and presumably viable, in the heart valves at the time of the patient's death.

*Penicillin Sensitivity* In vitro tests of the sensitivity of the organism to penicillin were made in enriched media under conditions most favorable for growth. Serial dilutions of penicillin were incorporated in the various media before inoculation with the streptobacillus, and, in every test, a good growth was obtained in the control tube. The tests were read at (approximately) 24, 48, and 72 hours. Although in certain media the organism will die off if not transplanted after 24 hours, in broth and thioglycolate enriched with serum, growth appeared between 24 and 48 hours in the higher dilutions of penicillin.

At 72 hours, the organism was completely inhibited by 0.1 unit of penicillin in all of the media used. This degree of penicillin sensitivity in vitro is of the same order of magnitude as is usually found by this technic for most of the non-hemolytic streptococci isolated from patients with subacute bacterial endocarditis.

*Virulence for Mice* Six mice\* were inoculated intraperitoneally with amounts of culture (seventieth generation) varying from 0.5 to 1.0 c.c. In three animals the inoculum was from a 4 per cent serum enriched broth culture, in the other three, washings from a blood agar slant were used. The animals were observed for 44 days, during which time there was no evidence of arthritis. Blood cultures (serum broth) on the third, fifth, seventh and seventeenth days, as well as cultures of heart's blood on the forty-fourth day, were all sterile. Another mouse, which had been inoculated intraperitoneally with 0.5 c.c. of an actively growing culture (approximately the twenty-fifth generation), developed no signs of arthritis and was alive three months after inoculation.

Brown and Nunemaker<sup>8</sup> emphasize the fact that after repeated passage (400 generations) on artificial media, the *Streptobacillus moniliformis* will lose its virulence for mice and will not regain it even after repeated animal passage. However, they routinely used about the fiftieth generation for the production in mice of chronic infection with arthritis and bacteremia. Therefore, it would seem that the strain isolated from this patient with a chronic infection was either truly avirulent for mice or lost its virulence on artificial media more rapidly than is usual.

## DISCUSSION

The postmortem findings in this patient were quite similar to those found when subacute bacterial endocarditis is caused by the implantation of a non-hemolytic streptococcus on a valve previously damaged by rheumatic fever. The clinical course also was identical with that customarily seen in subacute bacterial endocarditis, and quite unlike the usual *Streptobacillus moniliformis* infection, whether acquired through rat-bite, or in the form of Haverhill fever. It differed from the usual infection in the insidious onset, the absence of arthritis and the absence of a rash. (The joint symptoms experienced by the patient were apparently embolic in origin.) However, this case is quite similar in essential details to the case reported by Stuart-Harris and his associates.

Since one form of this markedly pleomorphic organism deceptively resembles a gram positive coccus both in culture and in tissue sections, it is possible that subacute endocarditis caused by it could be mistakenly regarded as streptococcal. For this reason, one might expect that the incidence of streptobacillus involve-

\* CFW, a virus-susceptible strain of mice, obtained from Carworth Farms, New City, New York.

ment of previously damaged heart valves is actually more frequent than is reflected by the single previous report<sup>7</sup>

For a detailed description of the biology of this organism, the recent authoritative monograph of Brown and Nunemaker<sup>8</sup> should be consulted. The *Streptobacillus moniliformis* is one of the most pleomorphic organisms known, and depending somewhat upon environmental factors, may appear as round bodies which simulate a coccus, or as long filaments. These may fragment, thus simulating chains of bacilli or cocci, or may show various fusiform or round swellings. In the strain isolated from our patient, the round coccal forms were gram positive, whereas the filamentous forms were gram negative. In addition to these forms, the streptobacillus can develop into a so-called L-1 or pleuropneumonia-like form. The exact morphology of this form is obscure because of its size, which is sufficiently small to allow passage through filters capable of holding back most bacteria. On solid media it forms colonies which are microscopic in size in early growth but later become visible macroscopically. Some controversy exists as to whether this L-1 form is a part of the life cycle of the streptobacillus or is a symbiont of it.<sup>9</sup> Brown and Nunemaker have reviewed the evidence pro and con, and, in the light of this and their own experiments, conclude that this pleuropneumonia-like microorganism is in fact one stage of the life cycle of the streptobacillus. They also believe that this L-1 form is the essential structure upon which the streptobacillus depends for survival, and that the organism usually exists in this L-1 form in infected human and animal tissues.

The streptobacillus will not grow in meat infusion broth unless it is enriched with serum or ascitic fluid. For this reason, as emphasized by Brown and Nunemaker, in patients with streptobacillus infections of the rat-bite or Haverhill type, blood cultures taken by the usual routine technics are seldom positive. The relative ease with which positive blood cultures were obtained from this patient is probably due to the fact that bacterial endocarditis was present, a lesion which usually makes positive cultures more readily obtainable than from bacteremias of other sources. The enrichment supplied to the primary cultures by the patient's own serum may have played some part, however, since all transplants from the original cultures to identical media which did not include this factor, were uniformly sterile.

Various chemotherapeutic agents have been used in the treatment of streptobacillus infections of man with indifferent success.<sup>3</sup> There is no evidence that the sulfonamide derivatives exert any therapeutic effect on human or animal infections with this organism.<sup>3, 10</sup> In a few instances of human infection, neoarsphenamine has been tried,<sup>3, 11, 12</sup> but no definite evidence of therapeutic effect was demonstrable, and it exerts no protection against the experimental infection in mice.<sup>10</sup> Brown and Nunemaker and Heilman found that various gold preparations (sodium aurothiomalate) had a striking effect on experimental infections in mice of the acute type. However, in the chronic type of experimental infection produced by less virulent (fiftieth generation) cultures of the streptobacillus gold therapy was without effect.<sup>3, 10</sup>

It is, therefore of considerable interest that the streptobacillus isolated from this patient with endocarditis was apparently inhibited by penicillin both in vitro and in the patient. Unfortunately, because of the lack of virulence for mice (by the twenty-fifth generation), it was impossible to investigate the effects of



penicillin on this strain in the experimental animal. Because of the existence of the L-1 form, more extensive investigations will have to be made before it can be concluded with certainty that the *Streptobacillus moniliformis* is completely inhibited by penicillin. However, further evidence to this effect has been supplied recently by Heilman and Herrell,<sup>18</sup> who found that mice infected with a young culture of streptobacillus all survived the acute infection when treated with penicillin. In a few of the survivors, arthritis developed, and in only one of 12 spleens examined from the treated group, were the organisms obtained by culture.

However, the possibility exists that penicillin may inhibit only the streptobacillus or "flowering" form of the organism's life cycle, while allowing the hardier L-1 form to survive. This question is under investigation at present.

It is impossible to decide whether this patient's endocarditis was significantly affected by the penicillin therapy. The clinical signs of infection disappeared promptly after treatment was begun, but valvular vegetations, in which the organisms could be demonstrated by staining, were still present after three weeks of therapy. It is conceivable that further penicillin therapy might have eradicated the infection of the valve, had not cardiac failure supervened. The development of cardiac failure, which is apparently due for the most part to the additional valvular damage caused by the bacterial infection, is not infrequently encountered in the sulfonamide or penicillin therapy of bacterial endocarditis, and is one of the important limiting factors in such therapy.

#### SUMMARY

A case of *Streptobacillus moniliformis* infection is reported, in which the clinical and postmortem findings were those of a subacute bacterial endocarditis, which had involved heart valves previously damaged by rheumatic fever. The literature concerning acute and subacute endocarditis caused by this organism is reviewed. Evidence that the organism was inhibited by penicillin is presented.

#### BIBLIOGRAPHY

- 1 BLAKL, FRANCIS G. The etiology of rat-bite fever, Jr Exper Med, 1916, xxiii, 39-60.
- 2 PLACE, E, and SUTTON, L E. Erythema arthriticum epidemicum (Haverhill fever), Arch Int Med, 1934, liv, 659-684.
- 3 BROWN, T MCP, and NUNEMAKER, J C. Rat-bite fever. A review of the American cases with reevaluation of etiology, report of cases, Bull Johns Hopkins Hosp, 1942, lxx, 201-327.
- 4 BLAKE, FRANCIS G, HORSTMANN, DOROTHY M, and ARNOLD, HILDEGARDE. A fatal case of rat-bite fever due to *Streptobacillus moniliformis*, Yale Jr Biol and Med, 1944, xvi, 589.
- 5 ROUNTREE, PHYLLIS M, and ROHAN, M. A fatal human infection with *Streptobacillus moniliformis*, Med Jr Australia, 1941, i, 359-361.
- 6 TUNNICLIFF, R, and MEYER, K. M. A case of rat-bite fever, Jr Infect Dis, 1918, xiii, 555-558.
- 7 STUART-HARRIS, C H, WELLS, A G, ROSHER, A B, MACKIE, F P, and WILSON, G S. Four cases of infective endocarditis due to organisms similar to *Haemophilus parainfluenzae*, and one case due to a pleomorphic streptobacillus, Jr Path and Bact, 1935, xli, 407-421.
- 8 SCHOTTMULLER, H. Zur Aetiologie und Klinik der Bisskrankheit, Dermat Wehnschr (supp), 1914, lviii, 77-103.

- 9 KLIENEGER, E The natural occurrence of pleuropneumonia-like organisms in apparent symbiosis with *Streptobacillus moniliformis* and other bacteria, Jr Path. and Bact, 1935, 21, 93-105
- 10 HEILMAN, F R Chemotherapy in experimental infections caused by *Streptobacillus moniliformis*, Science, 1940, xxi, 366-367
- 11 DICK, G F, and TUNNICLIFF, R A streptothrix isolated from the blood of a patient bitten by a weasel (*Streptothrix putorii*), Jr Infect Dis, 1918, xxiii, 183-187
- 12 SCHARLES, F H, and SEASTONE, C F, JR Haverhill fever following rat-bite, New England Jr Med, 1934, ccxi, 711-714
- 13 HEILMAN, F R, and HFRRELL, W E Penicillin in the treatment of experimental infections with *Spirillum minus* and *Streptobacillus moniliformis* (rat-bite fever), Proc Staff Meet Mayo Clin, 1944, xix, 257

## PRIMARY BRONCHOPULMONARY ASPERGILLOSIS, AN OCCUPATIONAL DISEASE \*

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ALTHOUGH pulmonary aspergillosis can no longer be considered a rare condition, in view of the increasing number of cases being reported in the literature, its consideration as a disease peculiar to certain occupations has been generally overlooked. Historically, the first recorded case is attributed to Hughes Bennett in 1842. In 1890 Dieulafoy, Chantmesse and Widal described several clinical cases in persons engaged as pigeon fatteners in Paris<sup>1</sup>. In 1897 Renon considered it as a trade disease in persons working as pigeon feeders. In this occupation the individuals engaged as pigeon stuffers crammed the beaks of the birds with a mixture of grain and water from their own mouths and some developed a severe form of mycotic pseudotuberculosis. He also considered pulmonary aspergillosis as a trade disease among the wigmakers who engaged in the task of combing the hair with rye meal to remove the fat<sup>2</sup>.

I wish to add another case to the growing literature. This case is unique in that, as far as I am able to determine, it is the first in the history of this country to be heard before the Industrial Commission of a sovereign state and to be declared as an occupational disease and, therefore, compensable under the laws of the state<sup>3</sup>.

### CASE REPORT

The patient D F, male, aged 47 years, was seen by me on January 7, 1942, and presented the following complaints: productive cough, shortness of breath and marked weakness of 10 years' duration, and inability to work because of these symptoms. About 10 years previously he began to cough and whereas at first it occurred only in occasional paroxysms, it became progressively more severe so that now it was constantly present. The cough had always been productive, occasionally of a black streaked expectoration, and had never been associated with hemoptysis. Coincidentally, he began to note some shortness of breath on effort, this, too, became progressively worse and was now constant, even at rest. These symptoms, together with weakness, loss of weight and anorexia, became so severe that it was difficult for him to engage in any work involving even the slightest effort.

\* Received for publication September 25, 1944

He was employed at the Union Stock Yards in varying capacities for approximately 20 years. His work at all times brought him into intimate and prolonged contact with animals and with heavy concentrations of dust, the dust of the Yards being mixed with that of hay, grain, corn and straw used for the animals. Part of the time he worked in the animal chutes, in the hog house, as yard master, as animal unloader and cattle yardener, etc.

Physical examination revealed a white male who was obviously dyspneic, even at rest. The face presented a florid cyanosis and audible rhonchi were evident at least five feet from the patient. The superficial veins of the anterior thorax were prominent and a bilateral respiratory lag was noted. Breathing was mainly of the abdominal type. Tactile fremitus was decreased, hyperresonance was obtained on percussion, and sibilant and sonorous râles were audible throughout both lungs. The heart was not enlarged, blood pressure was 115 mm Hg systolic and 80 mm diastolic and pulse 110 per minute.

Roentgen examination of the lungs showed emphysema with increased pulmonary linear striations, especially on the left side, adhesions of the left diaphragm near the cardiac apex, pleural thickening in the upper chest on both sides, especially the left, and massive lung root shadows, especially on the right.

Sputum examination and cultures were made and a typical *Aspergillus fumigatus* was isolated. The tuberculin patch test was definitely positive and a scratch test for *Aspergillus fumigatus* was questionably positive.

#### COMMENT

The history, physical examination and roentgen-ray study were indicative of a far advanced pulmonary fibrotic condition with pleural and bronchial involvement. The clinical picture resembled that of tuberculosis, but careful study here and elsewhere eliminated this diagnostic possibility because of the repeatedly negative sputa for tubercle bacilli and a conspicuous paucity of calcified shadows in the roentgenogram such as are often seen in chronic pulmonary tuberculosis. Careful questioning elicited the further facts that in June, 1941 he was studied at the Hines Veterans Hospital where a diagnosis of pulmonary aspergillosis was made and treatment instituted.

Proceedings were instituted before the Industrial Commission of the State of Illinois on the basis that the pulmonary affliction arose specifically out of the nature of the work being done for many years, i.e., the disease was peculiar to the occupation. The case was heard on arbitration on June 8, 1942, and the arbitrator's decision was filed with the Industrial Commission, giving an award to the petitioner. On review, the Industrial Commission upheld the award.<sup>3</sup>

#### DISCUSSION

Michaeli, in 1725, first described the genus *Aspergillus*, of the family Aspergillaceae, order Aspergillales, class Ascomycetes.<sup>4</sup> It is a regular inhabitant of soil and is frequently isolated from cereal products, unmilled grain, hay and other stock feeds, the spores being mingled with grains, seeds and flour. Of the many species of this mold, only a few are pathogenic. *Aspergillus fumigatus* is the most common offender in infections of the bronchopulmonary tissue.<sup>5</sup> However, occasional cases due to *Aspergillus niger* are reported.<sup>6,7</sup> Pigeons, canaries, penguins, ducks and chickens are most often affected. Man is relatively immune and classic instances are found in certain occupations which involve pro-

longed and intimate contact with grains or birds. Thus farmers, feed mill workers, and threshers are prone to infection. Certain dusts are also important, such as that developed in wig preparation and that produced by sponge cleaners who beat dried sponges.<sup>1</sup>

The principal factor in the pathogenesis of the disease in man seems to be exposure to repeated massive dosages. In such instances, the condition may be primary without any preceding pulmonary disease. Under other conditions, however, the factor of constitutional or local predisposition may be the determining one. Not infrequently, therefore, aspergillosis may be engrafted on previously diseased bronchopulmonary tissue as a secondary infection. Uncontrolled diabetes, dysentery, enteritis, cirrhosis and tuberculosis have been cited as predisposing causes,<sup>8</sup> as well as carcinoma<sup>9,10</sup> and bronchiectasis.<sup>7</sup> As a result of such association of diseases, the theory has been advanced that pulmonary aspergillosis does not develop in man unless local or constitutional resistance is lowered by some preexisting condition. That this is not necessarily true is attested to by the case herein reported and by the number of cases in the literature without evidence of any other pulmonary disease process.

### CONCLUSION

A case of primary pulmonary aspergillosis is herein reported in a man who worked at the Union Stock Yards for approximately 20 years. As far as can be determined, this is the first such case to be tried before the Industrial Commission of a sovereign state and to be declared an occupational disease.

### BIBLIOGRAPHY

- 1 VAN ORDSTRAND, H. SCOTT. Pulmonary aspergillosis, *Cleveland Clin Quart.*, 1940, vii, 66.
- 2 "Etude sur l'aspergillose chez les animaux et chez l'homme," Paris, 1897. Quoted by NORRIS and LANDIS, *Diseases of the chest*, 1938, W. B. Saunders Company, Philadelphia, p. 488, and by VAN ORDSTRAND.<sup>1</sup>
- 3 Daniel P. Ford v Union Stock Yards & Transit Co., No. O. D. 1767, Industrial Commission of Illinois.
- 4 MICHAELI. Quoted by STOLOW, ALAN J. Primary bronchopulmonary aspergillosis, *Jr Med Soc New Jersey*, 1939, xxi, 484.
- 5 MOOLTEN, SYLVAN E. A case of bronchopulmonary aspergillosis, *Jr Mt. Sinai Hosp.*, 1938, v, 29.
- 6 HETHERINGTON, L. H. Primary pulmonary aspergillosis, *Am Rev Tuberc.*, 1943, xlii, 107.
- 7 CARMIN, G. D. Secondary aspergillosis superimposed on bronchiectasis, *Jr Thoracic Surg.*, 1935, iv, 533.
- 8 DONALDSON, J. M., JR., KOERTH, C. J., and McCORKLE, R. S. Pulmonary aspergillosis, *Jr Lab and Clin Med.*, 1942, xxxii, 740.
- 9 KAMPMEIER, R. H., and BLOCK, H. A. Pulmonary aspergillosis in association with bronchial carcinoma, *Am Rev Tuberc.*, 1934, xxxv, 315.
- 10 EDWARDS, J. C. A baffling case of pulmonary carcinoma and aspergillosis. *New England Jr Med.*, 1935, lv, 213.

INTERLOBAR EFFUSION ASSOCIATED WITH CONGESTIVE  
HEART FAILURE \*

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PLEURAL effusion is common in congestive heart failure. Occasionally a small amount of the fluid may extend into an interlobar fissure from the general pleural space<sup>1</sup>. However, interlobar effusion may occur without any fluid in the pleural cavity. Only 14 such instances are found in a review of the literature<sup>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</sup>. The following case is reported to illustrate this unusual finding.

## CASE REPORT

A N, a white male, aged 59, was first admitted to the hospital on October 13, 1942, complaining of severe shortness of breath, cough and moderate epigastric pain. He was well until May, 1942, when effort dyspnea, orthopnea, cough, and ankle edema first appeared. The symptoms steadily increased in severity. Paroxysmal dyspnea and bouts of epigastric pain were present for one month before admission.

On physical examination the patient appeared dyspneic and slightly cyanotic. The respiratory rate was 26. The temperature was 98° F. The jugular veins were distended. The heart was found to be enlarged on percussion. The apical impulse was in the anterior axillary line in the sixth interspace. The rhythm was regular and the rate 140. A soft systolic and a diastolic murmur were present over the mitral area. The systolic blood pressure was 170 and the diastolic 110. Moist râles were present at the bases of both lungs. The liver was enlarged and tender. There was moderate edema of the feet and legs.

*Laboratory Examination* The red blood cell count was 3,910,000 and the hemoglobin 80 per cent. The white cells numbered 5,300, of which 75 per cent were polymorphonuclears, 19 per cent lymphocytes, and 6 per cent monocytes. The urine contained a trace of albumin and the specific gravity was 1.023. The non-protein nitrogen of the blood was 41 mg per 100 cc. The blood Wassermann and Kahn reactions were negative.

The electrocardiogram revealed a normal sinus rhythm, depressed ST<sub>1</sub>, inverted T<sub>1</sub>, a diphasic T<sub>2</sub>, elevation of ST<sub>4</sub>, and moderate left axis deviation.

A flat plate of the chest taken at a distance of six feet showed marked enlargement of the heart, slight clouding of both lung bases, and a sharply circumscribed shadow of increased density on the right side at the level of the interlobar fissure (figure 1). It measured 4 by 4 cm. On physical examination it was impossible to obtain any abnormal signs over the region comparable to the shadow.

*Course in Hospital* The patient received 3 grains of digitalis daily between October 13 and October 26 inclusive. Orthopnea, cough, paroxysmal dyspnea, edema, and recurrent epigastric pain persisted for one week. At the end of this time, there was moderate diuresis and a gradual disappearance of the signs and symptoms of congestive failure. On October 27, a second roentgenogram revealed that the shadow previously noted on the right side had disappeared leaving a slight thickening of the interlobar pleura between the upper and middle lobes of the lung (figure 2). The patient was discharged on November 18, 1942, free from symptoms except for slight effort dyspnea.

The patient was readmitted to the hospital on November 15, 1943, with severe dyspnea, cough, and slight edema of the lower extremities of three weeks' duration.

\* Received for publication September 1, 1944.

From the Medical Service of the Montefiore Hospital, Pittsburgh, Pennsylvania.

Physical examination revealed basal râles and enlargement of the liver. The systolic blood pressure was 152 mm Hg and the diastolic 114 mm Hg. The heart rate was 140 and the rhythm regular. Soft systolic and diastolic murmurs were present at the mitral valve area.

On November 15, a roentgenogram of the chest revealed a shadow in the interlobar space on the right side similar to that of the first admission (figure 3).

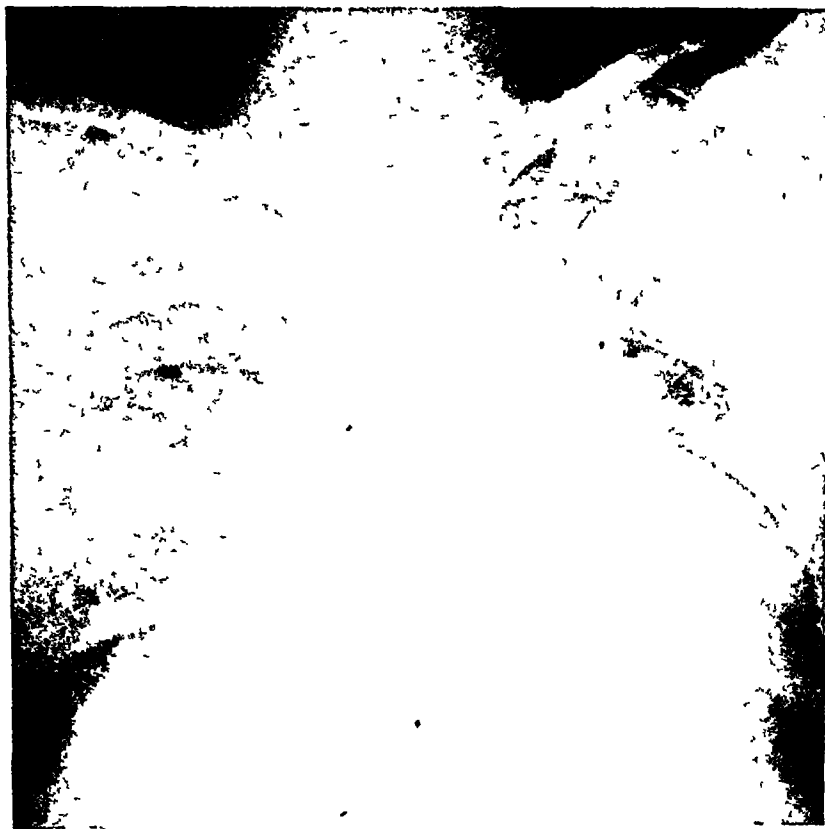


FIG 1 Roentgenogram of chest, October 21, 1943, shows circumscribed shadow of interlobar effusion in the right chest

Between November 15 and November 29 the patient received 9 grains of aminophylline daily without influencing the degree of heart failure. Roentgen examination on December 1 revealed no change in the size of the shadow. Eighteen grains of digitalis were administered between December 1 and December 4 together with 45 grains of ammonium chloride daily. Two c c of salyrgan were injected intravenously on December 4 and December 7 respectively. Following each injection the patient passed about 3,000 c c of urine. This was associated with disappearance of the signs and symptoms of heart failure. On December 8 a roentgenogram revealed a marked reduction of the shadow in the right chest (figure 4). The patient was discharged on December 23, 1943.

*Anatomy.* In order to understand the nature of this condition with its resultant clinical and roentgenological picture, an understanding of the anatomy of the interlobar fissures is important. The left lung is divided into two lobes by a single fissure. It begins dorsally about 5 cm below the apex, about the level of

the third rib, and extends downward and ventrally to the diaphragmatic surface of the lung. The right lung is divided into three lobes by two fissures. The main fissure is similar in its position to the fissure in the left lung. It separates the lower lobe from the middle and upper lobes. The other fissure begins in the main fissure on the dorsal part of the lung, and extends ventrally, ending at the level of the fourth rib. It separates the middle from the upper lobe of the lung.<sup>6</sup>

*Etiology* The serous type of interlobar effusion is usually due to a tuberculous infection of the lung, the purulent type is usually due to pneumonia. Other

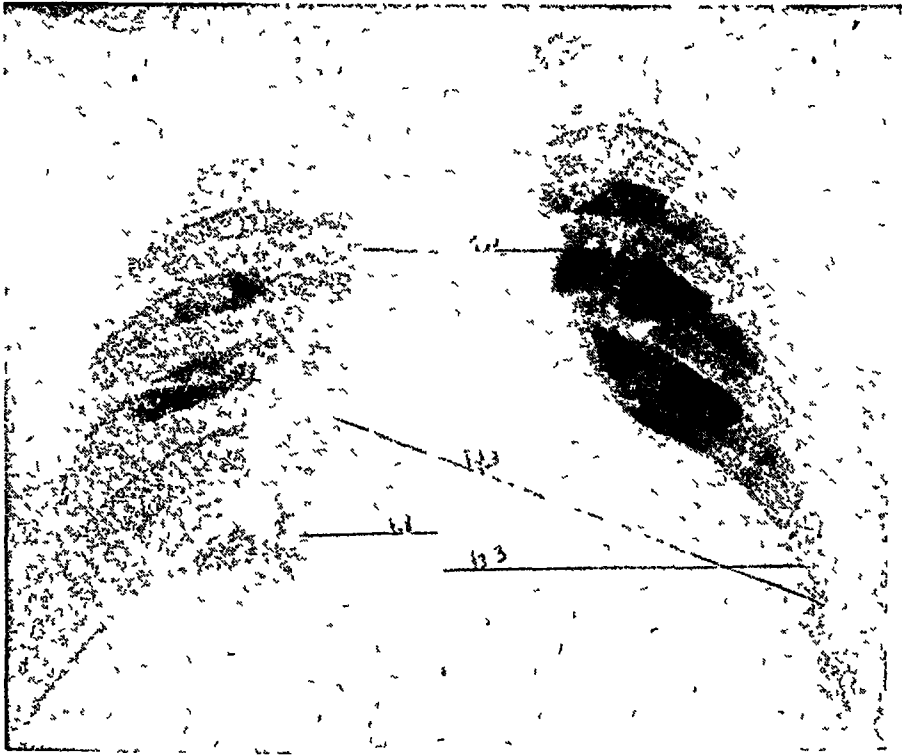


FIG 2 Roentgenogram of chest, October 27, 1943, shows disappearance of interlobar effusion in the right chest

less common causes of interlobar effusion are infections through the chest wall, and metastases through the blood or lymph stream from a distant focus of infection, such as tonsillitis, scarlet fever, puerperal infection, subphrenic abscess, etc.<sup>11</sup> Rarely interlobar serous effusion may be due to passive congestion as a result of heart failure.<sup>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</sup>

*Pathology* Necropsy of several reported cases of interlobar effusion associated with heart failure showed that fluid collected in the interlobar space because of either local adhesions<sup>9</sup> or because of an adhesive pleurisy which obliterated the entire pleural cavity with the exception of the small space between the lobes of the lung.<sup>4, 7</sup> The cause of the adhesions was a healed tuberculous lesion of the lung in one case<sup>9</sup> and unknown in the others.<sup>4, 7</sup>

*Clinical Picture* It is interesting to note that in almost all of the reported cases there was no history of past pulmonary or pleural infection to explain the presence of pleural adhesions.

The etiology of the heart disease in the reported cases was hyperthyroidism in one,<sup>8</sup> syphilis in one,<sup>9</sup> rheumatic fever in one,<sup>1</sup> coronary artery disease with or without arterial hypertension in five,<sup>1, 6, 7</sup> calcification and stenosis of the aortic valve, probably degenerative, in one,<sup>4</sup> and pericarditis of unknown etiology in one case.<sup>5</sup> It is clear that interlobar effusion may be associated with any type of heart disease, and that the prerequisites for its development are congestive heart failure in a patient with an antecedent, adhesive pleurisy.<sup>7</sup>



FIG 3 Roentgenogram of chest, November 15, 1943, shows shadow in the right chest similar to that of one year ago when the patient was in congestive failure

Clinically, it is impossible to recognize this condition because there are no characteristic signs or symptoms. The symptoms are due to congestive failure or to the underlying heart disease or to both. The amount of fluid is usually too small to produce symptoms or abnormal physical signs. Localized dullness and diminished breath sounds may occur in unusual instances<sup>9</sup> and suggest the possibility of this condition, but the diagnosis rests upon roentgen examination of the patient.

In all of the reported cases, as in our case, the effusion appeared on the right side, probably owing to the fact that fluid usually collects on this side in congestive failure.

*Roentgenogram.* Interlobar effusion produces a characteristic roentgen shadow. The location of the shadow depends upon the site of the fissure, and



upon what part of the fissure is occupied by fluid<sup>9</sup> The size and shape of the shadow will depend upon the amount of fluid present and upon the degree of compression of the adjacent lung Interlobar effusion usually causes a dense, sharply demarcated, homogeneous shadow. It may be round, oval, spindle-, wedge- or band-shaped<sup>1, 6</sup> The margins are sharp unless there is thickening of the adjacent pleura or disease in the adjacent lung

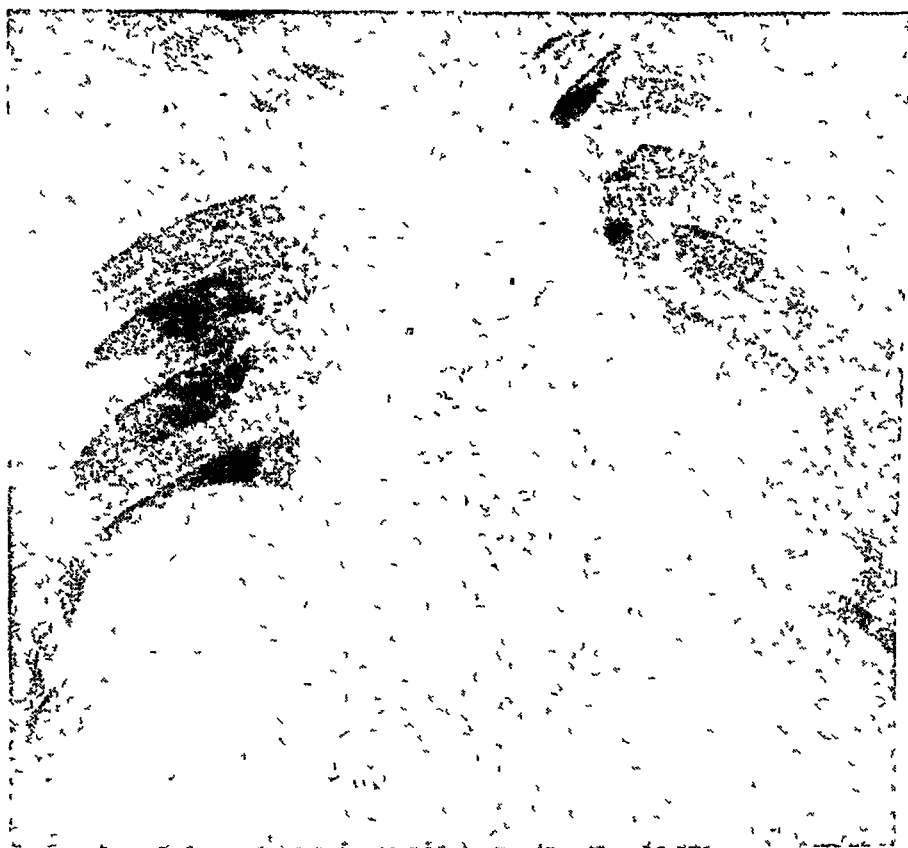


FIG. 4 Roentgenogram of chest, December 8, 1943, shows a marked reduction of the shadow in the right chest following the administration of diuretics

**Diagnosis** The roentgen shadow of interlobar effusion may simulate the appearance of interlobar empyema or of bronchiogenic carcinoma, metastatic neoplasm, pulmonary infarction, pneumonia, gumma or a localized caseating lesion situated in the region of the interlobar septum<sup>6</sup> The differential diagnosis will depend upon (1) the general clinical picture of the patient, (2) careful roentgen examination, and (3) the response to therapy

A lateral view of the chest may be necessary in differentiating an intrapulmonary lesion from interlobar effusion The lateral view will show that a part of the lobe is involved with the lesion ending at the interlobar septum<sup>6</sup>

Interlobar effusion due to heart failure will diminish or disappear shortly after the administration of a mercurial diuretic or an adequate amount of digitalis This change in the shadow coincides with diuresis On the other hand, the shadow may reappear with the reaccumulation of fluid, or with additional attacks of congestive heart failure In one reported case the shadow recurred and sub-

sided four times<sup>4</sup> The shortest interval between the initial attack and recurrence was 20 days,<sup>4</sup> the longest eight years<sup>7</sup>

In many of the reported cases, as in our case, the roentgenogram revealed a thickened pleura on the side of effusion, suggesting obliteration of the pleural space<sup>1, 4, 7</sup> In one case thickening of the pleura was indicated by the difficulty of performing thoracentesis<sup>7</sup> Interlobar effusion may be recognized by tapping the chest,<sup>9</sup> but this procedure is usually unnecessary since the diagnosis may be made simply by the administration of an effective diuretic

### CONCLUSIONS

Interlobar pleural effusion may be a manifestation of congestive heart failure The condition is due to the occurrence of congestive failure in a patient with an old adhesive pleurisy The diagnosis rests on finding roentgenographically a dense, sharply circumscribed shadow in the region of an interlobar fissure which disappears following the administration of a mercurial diuretic or digitalis The shadow is apt to reappear with the reaccumulation of fluid in the body

### BIBLIOGRAPHY

- 1 STEIN, IRWIN D, and SCHWEDEL, JOHN B Interlobar effusions in patients with heart disease, *Am Heart Jr*, 1934-1935, x, 230
- 2 FLEISCHNER, FELIX Das Rontgenbild der interlobaren Pleuritis und seine Differential-diagnose, *Ergebn d med Strahlenforsch*, 1926, ii, 199
- 3 HELM Cited by FELIX FLEISCHNER<sup>2</sup>
- 4 STEWART, H J Pleural effusion localized in an interlobar space, *Am Heart Jr*, 1928-1929, iv, 227
- 5 KISER, E F Pleural effusion associated with congestive heart failure localized in an interlobar space, *Am Heart Jr*, 1928-1929, iv, 481
- 6 FREEDMAN, EUGENE Roentgenological appearance of interlobar and mediastinal encapsulated effusion, *Radiology*, 1931, xvi, 14
- 7 STEELE, J M A report of two cases of localized pleural effusion in heart failure, *Am Heart Jr*, 1931-1932, vii, 212
- 8 VESSELL, H Interlobar pleural effusion in heart failure, *Med Jr and Rec*, 1932, cxvii, 576
- 9 AUSTRIAN, CHARLES R Encapsulated hydrothorax (hydrothorax saccatus interlobaris) in association with myocardial insufficiency, *Libman Anniversary Volumes*, 1932, ii, 101
- 10 ROESLER, HUGO Clinical roentgenology of the cardiovascular system, 2nd Edition, 1943, Charles C Thomas, Springfield, Illinois
- 11 CLAIRMONT, P Die interlobare Pleuritis, *Arch f klin Chir*, 1919, cxl, 335

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### HYPERTENSION CAUSED BY RENAL INFARCTION \*

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Or the numerous experimental investigations as to the pathogenesis of essential hypertension, the work of Goldblatt<sup>1</sup> is beyond doubt the most out-

\* Received for publication July 20, 1944

From the Medical Department of the Fairmount Hospital, Jersey City, N. J

standing. In a classical experiment he produced hypertension in the dog by constriction of one or both renal arteries with a silver clamp, with a resulting decrease in the blood flow through the kidney. These experiments have been repeated by other investigators with the same result. It is believed that a diminution in renal flow produces hypertension by the secretion of a pressor substance into the blood by the ischemic kidney. Since then a number of reports have appeared in the literature describing instances of unilateral infection of the kidney causing hypertension. Thus, Butler<sup>2</sup> reported two cases of unilateral pyelonephritis with hypertension in children in whom nephrectomy was followed by the return to normal blood pressure. Barker and Walters<sup>3</sup> reported five similar cases in ages ranging from 7 to 52 years. Richards<sup>4</sup> reported a case of unilateral renal tuberculosis associated with hypertension with a drop of blood pressure and relief of symptoms following the removal of the diseased kidney.

More akin to the Goldblatt experiment are the reports of cases in which an impediment to the flow of blood caused by a narrowing of the renal arteries has been responsible for the coexisting hypertension. A case of hypertension caused by constriction of the renal arteries by a lymphosarcoma was reported by Blatt and Page<sup>5</sup>. Persistent hypertension in a five-year-old child with an aneurysm of the left renal artery was described by Howard, Forbes and Lombcomb<sup>6</sup>. Koons and Ruch<sup>7</sup> reported a case of hypertension in a seven-year-old girl in whom a Wilms' tumor caused a compression of the renal artery with relief of the hypertension following the removal of the diseased kidney. Hochman<sup>8</sup> reported a case in which a syphilitic sacular aneurysm with compression and narrowing of the left renal vessels was accompanied by hypertensive vascular disease.

There are two reports in the literature describing instances of renal infarction as a cause of hypertension. The first report is by Prinzmetal, Hiatt and Tragerman<sup>9</sup> describing a case in which hypertension resulted from bilateral renal infarction. They showed that perfusates from the infarcted kidney of a patient with hypertension contained a pressor substance similar to that which is found in the ischemic kidneys of animals with clamped renal vessels. The second report is by Fishberg<sup>10</sup> who described four cases in which embolization of one or both renal arteries was followed by a rise in arterial tension.

However, the embolization in these five cases occurred at the time, or shortly after, they came under observation, so that an individual predisposition or a pre-existing hypertension could not be ruled out. The purpose of this report is to describe a case of hypertension caused by renal infarction in a patient who was under observation over a period of 12 years before embolization occurred. During this period hypertension was never noted. Furthermore, the patient recovered with a return to normal blood pressure which has remained normal two years following the infarction.

#### CASE REPORT

A M., single, white, female, aged 43 years, was admitted to the Fairmount Hospital on February 21, 1942, because of severe pain in the right loin and the right lower quadrant of the abdomen.

*Past History* She had rheumatic fever at the age of 12 and again at the age of 16. She was first seen on October 29, 1930, because of palpitation and slight dyspnea on exertion. Examination disclosed mitral stenosis and insufficiency and

an enlarged heart. The blood pressure was 130 mm Hg systolic and 76 mm diastolic. There was no change in her cardiac status until December 10, 1939, when auricular fibrillation was noted. She was digitalized and felt well on a maintenance dose of digitalis until her present illness. The blood pressure was normal throughout this period.

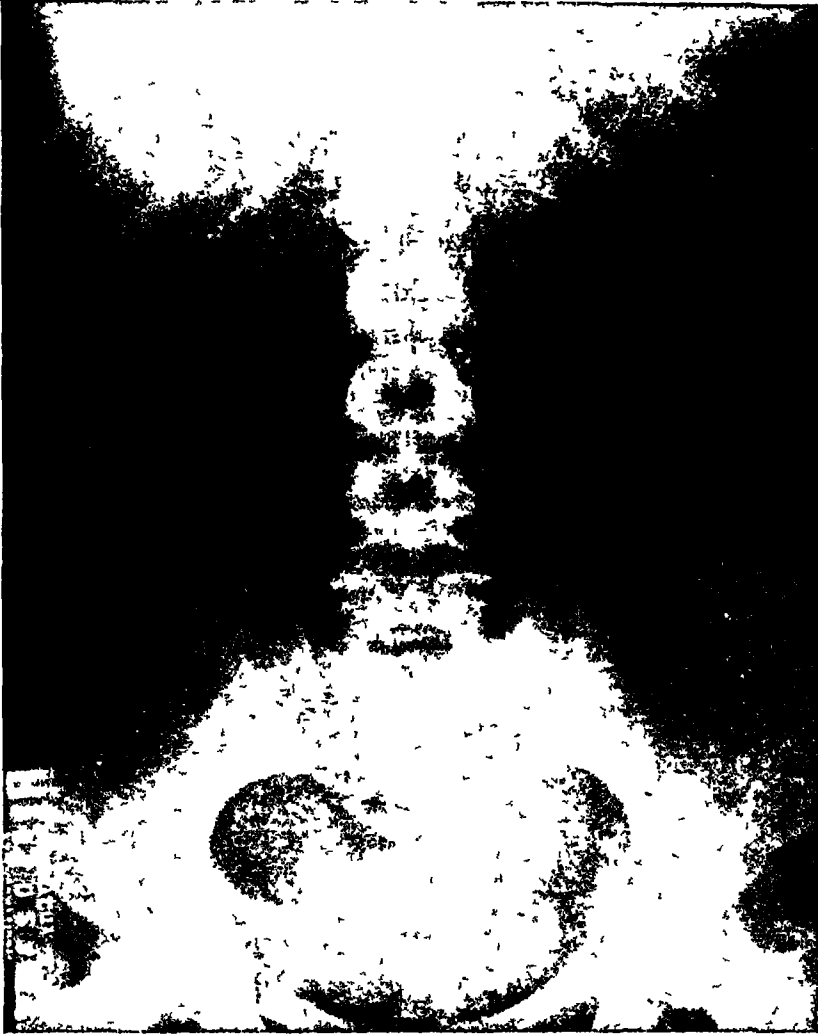


Fig 1 Intravenous urogram showing no function of the right kidney and normal function of the left kidney

*Present Illness* Twelve hours before admission, the patient suddenly felt severe pain in the right loin and the right lower quadrant of the abdomen. This was followed in a half-hour by vomiting. The pain, which was described as severe and cutting in character, began anteriorly and radiated to the right costovertebral region. It did not radiate to the perineum. At times she had pain all over the abdomen. For the first eight hours there was complete anuria. This was followed by hematuria.

Physical examination revealed a well-nourished woman in apparent distress. The veins of the neck were distended. The heart was enlarged to the left. Systolic and diastolic murmurs were heard at the apex. The second pulmonic sound was louder

than the aortic and accentuated. The rhythm was totally irregular. The ventricular rate was 168, the pulse rate, 126. There were crepitant râles in the bases of both lungs. The abdomen was distended. The liver was felt three fingers'-breadth below the right costal margin. The spleen was not felt. There was no ascites. There was marked tenderness with spasm over the right side of the abdomen, particularly the



FIG 2 Retrograde pyelogram showing no abnormality of the right pelvis and right ureter

right lower quadrant. There was marked tenderness to percussion over the right costovertebral angle. There was no peripheral edema. The temperature was 103.4° F. The blood pressure was 130 mm Hg systolic and 80 mm diastolic.

*Laboratory* The urine showed a specific gravity of 1.030, a 4 plus albumin, many red cells and a few white cells. The blood count revealed: red blood cells 4,610,000, hemoglobin 90 per cent, white blood cells 25,000. Differential count

Polymorphonuclears mature 72.5 per cent, band forms 6.5 per cent, small mononuclears 11.5 per cent, large mononuclears 2 per cent, transitionals 7.5 per cent. A blood examination on January 22 showed non-protein nitrogen 67 mg per 100 cc and sugar 130 mg per 100 cc.

| Date | Laboratory data   |
|------|---|
| 1/21 | Urine 4 plus alb, many red cells, few white cells                         |
| 1/22 | Non-protein nitrogen 70, leukocytosis                                     |
| 1/23 | Excretory urogram left kidney, normal function, right kidney, no function |
| 1/26 | Urine 3 plus alb, many red cells, few white cells                         |
| 1/28 | Retrograde pyelogram no abnormality of the right pelvis and right ureter  |
| 2/2  | Non-protein nitrogen 70, urine 3 plus alb, many red cells                 |
| 2/4  | Excretory urogram no function right kidney                                |
| 2/14 | Non-protein nitrogen 36, urine 2 plus alb, few red cells                  |
| 2/19 | Urine 1 plus alb, occasional red cell                                     |
| 2/20 | Excretory urogram normal function both kidneys                            |

Roentgen-ray examination of the chest on January 22 showed the heart to be greatly enlarged and of the mitral type. There was haziness and increased density throughout both lung fields.

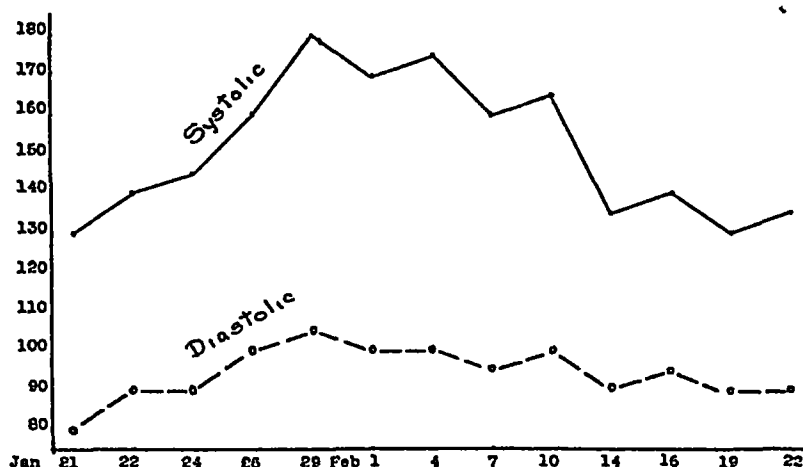


FIG 3 Graph showing elevation of arterial pressure following renal infarction, with subsequent return to normal

The electrocardiogram showed auricular fibrillation, ventricular extrasystoles, depression of  $ST_2$  and  $ST_4$ , inverted  $T_2$ ,  $T_3$  and  $T_4$ , and right axis deviation.

A flat plate of the abdomen did not reveal any abnormalities.

Excretory urogram (figure 1) performed on January 23 disclosed normal visualization of the left urinary tract but no visualization of the right side.

Cystoscopy was performed on January 28. There was prompt flow of indigo carmine with good concentration in five minutes on the left side, but no flow on the right side.

A retrograde pyelogram (figure 2) did not show any abnormalities of the pelvis or ureter of the right kidney.

*Course* The pain was severe for the first two days and then it began to subside. The tenderness and spasm also became less marked on the third day. The temperature ranged from  $101^\circ$  to  $103.4^\circ$  F for the first five days and then began to subside but there was a low grade fever for the following 15 days. On the sixth day following the infarction, the blood pressure rose to 160 mm Hg systolic and 100 mm diastolic.

The subsequent blood pressure readings are shown in the accompanying graph (figure 3)

On February 2 the non-protein nitrogen was 70 mg per 100 c c. An intravenous urogram on February 4 still showed no function on the right side. On February 16 the non-protein nitrogen was 36 mg per 100 c c. An excretory urogram on February 20 showed normal function of both kidneys. The patient was discharged improved on February 22. The blood pressure has remained normal in the two years following the infarction.

### COMMENT

A diagnosis of renal infarction was made on the basis of sudden severe pain in the right loin and right lower quadrant of the abdomen, followed by hematuria in a patient with mitral stenosis and auricular fibrillation. This diagnosis was confirmed by an intravenous urogram showing no function in the right kidney, and by a retrograde pyelogram showing no abnormalities in the pelvis or ureter of the same side. On the sixth day following the infarction, the blood pressure became elevated to 160 mm Hg systolic and 100 mm diastolic, and reached 180 mm Hg systolic and 106 mm diastolic on the twelfth day. The blood pressure remained elevated for 21 days and then returned to its previous level. The function of the kidney returned to normal at the same time.

### SUMMARY

A case is presented with mitral stenosis and auricular fibrillation in which an embolus in the right kidney resulted in elevation of the arterial pressure. The blood pressure returned to normal with the disappearance of symptoms of renal infarction.

### BIBLIOGRAPHY

- 1 GOLDBLATT, H., LYNCH, J., HANZAL, R. F., and SUMMERVILLE, W. W. Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia, Jr. *Exper Med*, 1934, lix, 347-379.
- 2 BUTLER, A. M. Chronic pyelonephritis and arterial hypertension, Jr. *Clin Invest*, 1937, xvi, 889-897.
- 3 BARKER, NELSON W., and WALTERS, WATMAN. Hypertension and chronic pyelonephritis results of nephrectomy, Jr. *Am Med Assoc*, 1940, cxv, 912-916.
- 4 RICHARDS, G. GILL. Unilateral renal tuberculosis associated with hypertension, *Ann Int Med*, 1941, xv, 324-328.
- 5 BLATT, EBNER, and PAGE, IRVINE H. Hypertension and constriction of renal arteries in man, report of case, *Ann Int. Med*, 1939, xii, 1690-1699.
- 6 HOWARD, T. L., FORBES, R. P., and LIPSCOMB, W. R. Aneurysm of left renal artery in a child five years old with persistent hypertension, Jr. *Urol*, 1940, xlv, 808-815.
- 7 KOONS, K. M., and RUCH, M. K. Hypertension in a seven year girl with Wilms' tumor relieved by nephrectomy, Jr. *Am Med Assoc*, 1940, cxv, 1097-1098.
- 8 HOFFMAN, BYRON J. Renal ischemia produced by aneurysm of abdominal aorta, Jr. *Am Med Assoc*, 1942, cxix, 1028-1030.
- 9 PRINZMETAL, MYRON, HIAAT, NATHAN, and TRAGERMAN, L. J. Hypertension in a patient with bilateral renal infarction, Jr. *Am Med Assoc*, 1942, cxviii, 44-46.
- 10 FISHERBERG, ARTHUR M. Hypertension due to renal embolism, Jr. *Am Med Assoc*, 1942, cxix, 551-553.

## SPONTANEOUS HEMOPNEUMOTHORAX REPORT OF A CASE OCCURRING IN A SOLDIER \*

By JOHN FRANKLIN, Capt, M C, A U S, *Hunter Field, Georgia*

THE true incidence of spontaneous hemopneumothorax is unknown. Whereas the literature contains reports of sporadic cases, many cases are not reported, and many cases are misdiagnosed as hydropneumothorax, when roentgen evidence of fluid alone is accepted without the benefit of a diagnostic thoracentesis. In 1937, Hopkins<sup>1</sup> collected 43 cases from the literature and reported three cases of his own. Hartzell<sup>2</sup> in 1942, reported 40 selected cases from the literature and three cases observed at Cleveland City Hospital during the preceding 10 years. The apparent rarity of this complication of spontaneous pneumothorax prompts me to report the following case.

### CASE REPORT

M A H, aged 23, Private First Class, United States Army, was admitted to the Station Hospital, Hunter Field, Georgia, on August 27, 1943, complaining of severe upper abdominal and right chest pain. The admitting diagnosis was acute cholecystitis.

*Family History and Past History* The patient's mother had pulmonary tuberculosis during the period of the patient's adolescence. The patient was employed as a potter for three years during after-school hours from 1937 to 1940. The atmosphere was very dusty and he coughed frequently and experienced frequent epistaxes. Two years before admission he had an attack of right pleuritic pain lasting one week which was associated with a slight dry cough, but no chills or fever. During the two months prior to admission the patient complained of pain at the left costal margin, exaggerated by exercise. His dispensary record carried the diagnosis of intercostal neuralgia. No chest roentgenogram was taken. He had been thin since birth but capable of normal physical exertion. However, during the previous eight months of service this soldier felt under par and fatigued easily. The chest roentgenogram upon induction one year prior to admission was reported clear. As the soldier was on limited service because of frequent attacks of migraine headache, he was not subject to strenuous physical exertion.

*Present Illness* The present illness began one week prior to admission when the patient developed a recurrence of pleuritic pain over the right anterior chest, similar to the pain noted two years previously. Pain was so severe that he sought relief on sick call. Physical examination at this time revealed the chest and heart to be normal. No roentgenogram of the chest was made. The night of admission the patient experienced severe pain over the right anterior chest which radiated to the right upper abdominal quadrant and to the right shoulder. Breathing became shallow and difficult and shortly after this he became nauseated and vomited several times.

*Physical Examination* Temperature 100° F. Pulse 110. Respirations 30. Blood pressure 90 mm Hg systolic and 70 mm diastolic. The patient appeared acutely and seriously ill. There was a marked sallow yellow color to the skin and pallor of the mucous membranes. Respirations were rapid, labored and shallow and the patient held his right side as he breathed. There was no cough. He was quite thin and underweight.

Significant findings were limited to the chest and abdomen. The trachea was markedly displaced to the left. There was an inspiratory lag which involved the entire right chest. The intercostal spaces on the right were distended. There was

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The subsequent blood pressure readings are shown in the accompanying graph (figure 3)

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- 1 GOLDBLATT, H, LYNCH, J, HANZAL, R F, and SUMMERVILLE, W W. Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia, *Jr Exper Med*, 1934, lxx, 347-379.
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increased precordial activity and a prominent cardiac impulse could be seen in the fourth and fifth left interspaces at the anterior axillary line. The percussion note over the right chest was hyperresonant and the normal hepatic dullness was obscured in the supine position. In the upright position flatness to percussion was present from the eighth rib down posteriorly on the right. Breath sounds, vocal and tactile fremitus were absent over the entire right chest. The heart sounds were of good quality. There was a loud high pitched systolic murmur over the entire precordium. The abdomen was held rigidly and deep palpation was resisted. The liver could be percussed two fingers' breadth below the costal margin. There was exquisite right upper quadrant tenderness.

*Laboratory Results* A chest roentgenogram confirmed the original clinical impression of a hydropneumothorax. There was complete collapse of the right lung, with a fluid level approximating the eighth rib posteriorly. The trachea and heart were displaced to the left and herniation of the mediastinum had occurred (figure 1).



FIG 1 Chest roentgenogram taken on admission showing complete collapse of the right lung, a fluid level approximating the eighth rib in the posterior axillary line, displacement of the trachea and heart to the left, and herniation of the mediastinum and right lung due to the pressure of the air in the right pleural cavity.

A diagnostic thoracentesis resulted in the removal of air and blood under pressure. Approximately 700 c.c. of air were removed and 25 c.c. of blood with a red cell count of 3,160,000 and a white cell count of 6,900. The fluid was sterile. Smear, culture and guinea pig inoculation failed to reveal the presence of acid fast bacilli. Pleural pressure was not recorded. The patient's red cell count was 4,310,000, with a hemoglobin of 11.5 grams and a white cell count of 15,650. The differential revealed a shift to the left. The urine was normal.

*Course, and Treatment* The patient experienced immediate relief of his respiratory distress with the removal of air from the right chest. There was a noticeable shift of the mediastinum toward the midline following this procedure (figure 2A). The incipient shock was treated by the administration of intravenous glucose and saline followed by two 500 cc transfusions of Type B blood. The blood pressure rose to 105 mm Hg systolic and 70 mm diastolic where it remained. Morphine was required only during the first 24 hours to control the patient's pleural pain and anxiety. The liver receded above the costal margin and the right upper quadrant tenderness subsided with the relief of the tension pneumothorax. With the return of the mediastinum to the midline, the systolic murmur disappeared. A pleural pressure reading at this time indicated a pressure of 0 to +5 and 200 cc air were removed to bring the pressure to atmospheric level. At no time subsequently did the pleural pressure rise above +5 and sufficient air was removed from time to time to maintain the mean pressure at 0.

On the second hospital day the patient's temperature rose to 104° F and for two days thereafter ranged between normal and 102° F. Thereafter the fever fell by lysis and was normal by the ninth hospital day. Pulse and respirations became normal during the same period.

On alternate days beginning on the third hospital day, four thoracenteses resulted in the removal of a total of 2,700 cc of grossly bloody fluid showing a decreasing red cell count from 3,160,000 to 510,000 and a rising relative eosinophile count from 18 per cent to 43 per cent. The fluid white cell count never rose above 9,850. In each instance the fluid obtained was sterile. Search for acid fast bacilli was made and none was found. Culture and guinea pig inoculations were done by the Fourth Service Command Laboratories and all results were negative for tuberculosis. The patient's originally high blood count probably reflected dehydration as, following the administration of intravenous fluid and despite two transfusions, the red cell count fell to 3,780,000 and the hemoglobin to 10.5 gm. This gradually rose to normal with the stimulus of a high caloric and high vitamin diet and supplemental iron. At no time did the patient reveal clinical icterus.

Progressive chest roentgenograms (figure 2) showed a decreasing fluid level and progressive reexpansion of the right lung. The lung at the last examination had entirely reexpanded, the costophrenic angles were clear, and there were no parenchymal changes to suggest pulmonary tuberculosis. An intradermal test using second test strength (0.005 mg) PPD was negative after 48 hours. The patient was considered cured and returned to duty after a period of convalescence.

### DISCUSSION

Although the equilibrium of increased pleural pressure and lowered blood pressure is probably effective in controlling bleeding, the respiratory embarrassment and incipient circulatory collapse occasioned by the acute and massive loss of blood in this case, plus the marked mediastinal displacement, forced us to relieve the pleural tension and replace the blood loss. It is difficult to estimate accurately the acute blood loss. A total of 2,700 cc of bloody fluid was removed containing both serum and whole blood. The red cell count of the original fluid removed was comparable to that of the systemic blood discounting the effect of dehydration from protracted vomiting as well as the loss of blood volume. At the time of the first thoracentesis there was no clinical or roentgenographic evidence of continued bleeding. As the patient's body weight was about 57 kilograms, the blood lost was probably in excess of 30 per cent of his blood volume estimating the latter at 4 $\frac{3}{4}$  liters. The acute loss of 30 per cent of one's

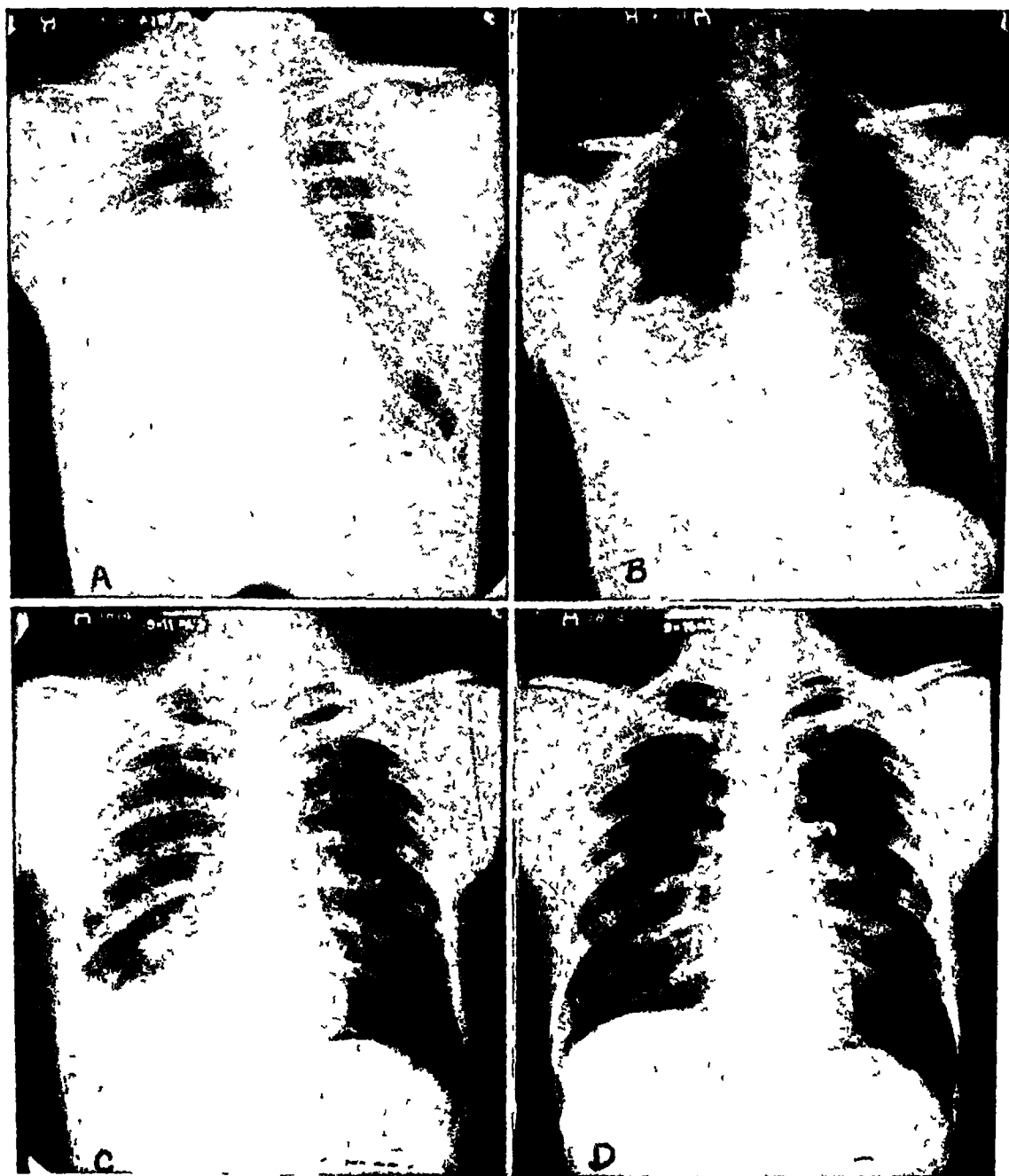


FIG 2 (A) Portable roentgenogram taken on the second hospital day following the removal of 1100 cc of air from the right pleural cavity showing a decided shift of the trachea, heart and mediastinum toward the midline with a consequent displacement of the fluid and rise in the fluid level (B) Portable roentgenogram taken on the fifth hospital day after the removal of 1,200 cc of grossly bloody fluid showing incomplete reëxpansion of the right upper lobe and a fall in the fluid level The heart and mediastinum are centrally located (C) Roentgenogram taken on the sixteenth hospital day showing complete reëxpansion of the right lung except at the extreme right apex where an irregular radiolucent area suggests the presence of an emphysematous bleb The right costophrenic sinus and diaphragm are still hazy (D) Roentgenogram taken on the twenty-first hospital day showing complete reëxpansion of the right lung and complete reabsorption of fluid The area previously described at the right apex now appears to be only thickened pleura There are no parenchymal changes to suggest active pulmonary tuberculosis

blood volume is considered the limit beyond which the physiologic mechanisms of replacement fail. Consequently, the replacement of fluid and whole blood was indicated.

This case falls into the category of those variants in the clinical picture of hemopneumothorax in which the signs and symptoms are referred to the abdomen. The presence of right upper quadrant pain and tenderness, radiation of pain to the right shoulder, nausea and vomiting, and sallow yellow pallor suggestive of icterus was indeed confusing. It is interesting to note that the admitting diagnosis was acute cholecystitis.

The pathogenesis of this instance of hemopneumothorax was not determined. Despite a strong family history of tuberculosis and a suggestive past history of chronic disease, no evidence of tuberculosis could be found. The work of Kjaergaard,<sup>3</sup> Hamman,<sup>4</sup> Kirsner,<sup>5</sup> and others offer many explanations for spontaneous pneumothorax. The presence of ruptured emphysematous blebs has been observed in several cases of hemopneumothorax which have come to the autopsy table, and pleural bullae also have been demonstrated radiologically. These constitute a ready source for the escape of air into the pleural cavity and one needs but postulate the presence of a valve vesicle to explain a tension pneumothorax. The source of the bleeding may well be from the ruptured vesicle itself as Mazzei and Pardal<sup>6</sup> have shown these bullae to be richly vascularized. A more likely possibility is that bleeding results from an adhesion torn by the traction of the collapsing lung. Adhesions are frequent<sup>7</sup> and this source of bleeding is relatively common in artificially induced pneumothorax.

#### SUMMARY

A case of benign spontaneous hemopneumothorax has been presented in which the presenting symptoms and signs were referred to the abdomen. The treatment and probable etiology have been discussed.

#### BIBLIOGRAPHY

- 1 HOPKINS, H. U. Spontaneous hemopneumothorax, report of three cases with a review of the literature, *Am. Jr. Med. Sci.*, 1937, **CXLIII**, 763-772.
- 2 HARTZELL, H. C. Spontaneous hemopneumothorax, report of three cases with a review of the literature, *Ann. Int. Med.*, 1942, **XXII**, 496-510.
- 3 KJAERGAARD, H. Spontaneous pneumothorax in the apparently healthy, 1932, Levin and Munksgaard, Copenhagen.
- 4 HAMMAN, L. A note on the mechanism of spontaneous pneumothorax, *Ann. Int. Med.*, 1939, **LIII**, 923.
- 5 KIRSNER, J. J. Spontaneous pneumothorax, etiologic considerations, *Am. Rev. Tuberc.*, 1939, **IX**, 477.
- 6 MAZZEI, E. S., and PARDAL, R. Le pneumothorax spontané bénin, *Paris med.*, 1934, **CXXX**, 509.
- 7 LEOPOLD, S. S., and LIEBERMAN, L. M. The present status of artificial pneumothorax in the treatment of lobar pneumonia, *Ann. Int. Med.*, 1935, **IX**, 19.

## MULTIPLE FRACTURES OF RIBS BY COUGH: REPORT OF A CASE \*

By OSCAR SWINEFORD, JR., M.D., F.A.C.P., and JOHN MCKINNON, M.D.,  
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FRACTURE of one or more apparently normal ribs by cough was first described by Graves<sup>1</sup> in 1834. Tunis<sup>2</sup> found 25 cases in the literature in 1890. Atkinson,<sup>3</sup> Seilin,<sup>4</sup> Webb and Gilbert,<sup>5</sup> and Brewster<sup>6</sup> added seven cases. Halliwell,<sup>7</sup> Howson,<sup>8</sup> and Richardson,<sup>9</sup> each reported four such fractures in a single case. The report of Sabbione,<sup>10</sup> in Italian, was not read. Oechsli<sup>11</sup> found 12 cases in 2,000 patients with pulmonary tuberculosis, an incidence of 0.6 per cent. Richardson<sup>9</sup> found 20 cases in 1903 patients with tuberculosis. The incidence was 0.8 per cent in incipient, 2 per cent in moderately advanced, 6.5 per cent in far advanced cases. He thinks such fractures are much more common than is generally appreciated. He points out that they are usually small linear breaks which are not very obvious in roentgenograms until callus forms. The symptoms are those of pleurisy and they occur in patients in whom pleurisy would be expected. He thinks bony decalcification due to tuberculosis is a contributory factor.

Fractures of ribs by cough have been found in association with "chronic bronchitis," asthma, foreign body in the larynx, and in pulmonary tuberculosis.

The following case is presented because it is the largest number of ribs fractured by coughing in a single individual, because there was no demonstrable evidence of decalcification nor of bone disease, and because the cough was due to simple bronchitis and not to tuberculosis.

### CASE REPORT

A 35 year old housewife had had repeated winter respiratory infections since adolescence. They had been particularly troublesome during the past four years. The usual respiratory infections began in November 1943. Several weeks later she had an acute pain in the left lower axillary area. This had the characteristics of a rather severe pleural pain. Roentgenograms showed no abnormalities in the chest, nor in the ribs, except some thickening of the bronchial markings. She continued to have remissions and exacerbations of the cough, low grade fever, and severe pleural type of pain.

Two weeks before admission, our first examination, she developed another severe cough with pain in the left lower chest increased by cough and respirations. No abnormal signs were heard in the chest. She began treatment for purulent sinusitis of the antra, by lavage, on April 14, 1944. She had had a mild fever for several days. The pain subsided in a few days but the cough persisted.

Three days before admission on April 24, 1944 she had another episode of severe pleural pain in the right lower chest. In the hospital she was found to be very poorly nourished. She was coughing frequently and vigorously. Each cough and each inspiration produced severe right lower chest pain. The respiratory motions were splinted on the right. The eighth right rib area was quite tender. A loud pleural rub was heard under the area of tenderness.

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Roentgenogram of the chest showed transverse fractures of the left sixth and seventh and of the right eighth ribs with callus. In addition the left eighth and the right tenth ribs were fractured incompletely near the mid-axillary lines. The bronchial markings in the bases were quite heavy suggesting either severe bronchitis or early bronchiectasis. Roentgenograms of the sinuses showed pansinusitis. There was no evidence of decalcification of the skull, ribs nor vertebrae. Chest films made in 1940 and 1930 were available for comparison. There was no history of injury. The serum calcium was 10 mg per 100 c.c., blood phosphorus 4.4 mg per 100 c.c., serum phosphatase 4.4 units. The plasma total protein was 6.5 gm per 100 c.c. The tuberculin test was and had been repeatedly negative. Fasting plasma vitamin C was 1.2 mg per 100 c.c. The sternal bone marrow showed no abnormalities. A biopsy of the right fourth rib showed normal cancellous bone.

On June 5 she fractured another rib. Films of the chest June 6 showed (figure 1) six calluses and one linear fracture. Another fracture on June 9 made a total of eight fractures.



FIG 1 Arrows point to the rib fractures with callus formation and to the linear fractures

Roentgen therapy plus lavage of the antra produced marked improvement in the cough and in the sinuses. The antra washed clear and were clear in a roentgenogram on June 6, 1944. She had had about 150 multi-vitamin capsules in six weeks when the seventh and eighth fractures occurred.

#### SUMMARY AND CONCLUSIONS

A case is reported in which eight apparently normal ribs were fractured by cough within six months. The patient had bronchosinusitis. She was very thin. There was no evidence of tuberculosis. Multi-vitamin therapy plus milk-



in abundance did not prevent additional fractures. The symptoms were indistinguishable from pleurisy. A pleural rub was heard with only one of the last four fractures. Moderate tenderness over the fracture was the most suggestive physical sign. Until callus forms only careful search of roentgen films may disclose the usually linear breaks. Fractures of ribs by cough are probably more frequent than is realized.<sup>9</sup> They must be thought of whenever there is pleuritic pain plus tenderness. The literature is reviewed.

#### BIBLIOGRAPHY

- 1 GRAVES, R. J. Fracture of a rib produced by a violent fit of coughing, *Am Jr Med Sci*, 1834, xiii, 553-554
- 2 TUNIS, J. P. Rib fracture from muscular action, with forty collected cases, *University Med Magazine*, 1890-91, iii, 57-65
- 3 ATKINSON, A. Fracture of rib during cough, *Brit Med Jr*, 1898, i, 490
- 4 SEILIN, J. Fracture of the eleventh rib by muscular action, resume of reported cases, *Med Rec*, 1917, xci, 281-283
- 5 WEBB, G. R., and GILBERT, G. B. Ribs fractured by cough, *Jr Am Med Assoc*, 1923, lxxxI, 25
- 6 BREWSTER, E. S. An unusual case of fracture of the rib, *Med Rec*, 1939, ci, 159-160
- 7 HALLIWELL, B. T. Fracture of ribs caused by coughing, *Brit Med Jr*, 1929, ii, 1056
- 8 HOWSON, C. R. Rib-fracture by cough, case, *Am Rev Tuberc*, 1934, xxx, 566-567
- 9 RICHARDSON, E. C. Indirect fracture of the rib in pulmonary tuberculosis, *Jr Am Med Assoc*, 1936, cvi, 1543-1544
- 10 SABBIONE, C. Radiological study of spontaneous rib fracture among tuberculous, *Radiology*, 1939, xxxii, 127 (Abstract)
- 11 OECHSLI, W. R. Rib fracture from cough. Report of twelve cases, *Jr Thoracic Surg*, 1936, v, 530-534

## EDITORIAL

### *IMMUNITY AND IMMUNOLOGICAL REACTIONS IN MUMPS*

THE etiologic agent in mumps was first isolated by Johnson and Goodpasture<sup>1</sup> and by Findlay and Clarke<sup>2</sup>. These investigators were able to reproduce the disease in monkeys (*Macacus*) by injecting into the parotid duct saliva from human cases of mumps obtained during the first or second day of the disease. They demonstrated that the agent was a filtrable virus which was present in the saliva of the patients and in the tissue of the infected parotid glands of the monkeys. They also found that after recovery the monkeys were immune to reinoculation. Until recently, however, little was known as to the mechanism of the immunity, nor were there available specific methods of diagnosis or procedures which would determine immunity or susceptibility in human beings.

Although mumps is usually a mild infection with a very low mortality, it is highly contagious and spreads rapidly when introduced into closed communities of susceptible individuals such as schools or military establishments. Under these conditions it causes a serious, if temporary, loss of manpower, particularly in those cases with disabling complications like orchitis or meningoencephalitis. In such situations effective measures of control would be of great practical value. Recent work by Enders, Kane and their associates has contributed materially to this end. These investigators<sup>3</sup> reproduced the disease regularly in monkeys by the method used by Johnson and Goodpasture. In parotid glands removed by operation a few days after inoculation they demonstrated the presence of active virus, often in high concentration, even in animals in which little or no enlargement of the parotids was evident clinically. They were unable to demonstrate the virus in any other tissues or organs of the infected monkeys, nor to cause infection or demonstrate multiplication of the virus after inoculation by any other route. Attempts to demonstrate virus-neutralizing activity in the pooled serum of convalescent human cases gave somewhat equivocal results. In three experiments virus was demonstrated by complement fixation tests in the parotid glands of the "protected" animals, but the titer was much lower than in the controls. It is probable, therefore, that some neutralizing power was present.

By using suspensions of infected parotids as antigen, however, they were able to demonstrate complement-fixing antibodies in the serum of infected monkeys after recovery in practically every case. In some animals it could

<sup>1</sup> JOHNSON, C. D., and GOODPASTURE, E. W. Investigations of etiology of mumps, *Jr Exper Med*, 1934, LXV, 1-19.

<sup>2</sup> FINDLAY, G. M., and CLARKE, L. P. Experimental production of mumps in monkeys. *Brit Jr Exper Path*, 1934, VI, 309-313.

<sup>3</sup> ENDERS, J. F., KANE, L. W., COHEN, S., and LEVINS, J. H. Immunity in mumps. I. Experiments with monkeys (*Macacus mulatta*). The development of complement-fixing antibody following infection and experiments on immunization by means of inactivated virus and convalescent human serum, *Jr Exper Med*, 1945, LXXVI, 93-117.

be demonstrated (in low titer) within a few days after inoculation, and in most animals it was present in high titer by the end of the second week. After about one month the titer fell, but in some cases significant amounts remained after 10 to 21 months. No antibody was found in normal monkeys, but in a few cases antibody appeared in monkeys which had been in casual contact with infected animals, although no clinical manifestations of infection had been recognized.

By the same method these workers<sup>4</sup> demonstrated the regular appearance of complement-fixing antibody in the serum of human convalescent cases. In a few cases it appeared or was present in low titer at the onset of clinical manifestations of infection but increased markedly in titer during convalescence. In those cases which were tested early, it was absent before and (usually) at the onset of the disease, but reached high titers during the second and third weeks. This persisted in lower titer for months, in three of four cases tested it was present two years after the infection.

The reaction appears to be useful in the recognition of atypical cases of infection without obvious involvement of the salivary glands. In a study of 51 patients showing clinical manifestations of meningoencephalitis,<sup>5</sup> positive reactions were obtained in all of 17 cases which showed enlargement of the salivary glands. In 16 of the cases without involvement of the salivary glands, positive reactions were also obtained, whereas in 18 others, clinically indistinguishable, the reaction was negative, and some other etiological agent presumably was concerned.

In most normal individuals without a history of mumps, the complement fixation reaction was negative. It was also negative in all of a number of cases suffering from other types of infection. In some cases, however, a positive reaction was obtained although no previous attack of mumps was known to have occurred. Since all other available evidence indicates that the reaction has a high degree of specificity, it seems probable that these individuals had had an atypical or subclinical attack of the infection. That this may occur is indicated by observations on a laboratory worker who was handling mumps virus and whose complement fixation reaction, previously negative, became positive under observation, although there was no clinical evidence of illness.

Since it was found possible to destroy the infectivity of a virus suspension without loss of the antigenic power, this material could be used to determine the presence of cutaneous hypersensitivity in convalescent cases. In a preliminary study of a small group of normal individuals, intracutaneous injection of inactivated virus caused no reaction before infection or during the acute phase. The reaction became positive in all these cases during con-

<sup>4</sup> ENDERS, J. F., COHEN, S., and KANE, L. W. Immunity in mumps. II. The development of complement-fixing antibody and dermal hypersensitivity in human beings following mumps, *Jr Exper Med*, 1945, lxxxi, 119-135.

<sup>5</sup> KANE, L. W., and ENDERS, J. F. Immunity in mumps. III. The complement fixation test as an aid in the diagnosis of mumps meningoencephalitis, *Jr Exper Med*, 1945, lxxxi, 137-150.

valescence at intervals varying from one week to three months. The appearance of a positive reaction was also observed following an inapparent infection. The hypersensitivity in most instances lasted at least one and one-half to two years. There was no relationship between the presence of complement-fixing antibody in the serum and the cutaneous hypersensitivity. The latter appeared later in convalescence and in some cases at least persisted longer than the complement-fixing antibody. In a few cases, however, cutaneous hypersensitivity failed to develop or disappeared more quickly after an attack.

The possibility of active immunization from mumps was also investigated. Monkeys were injected subcutaneously with virus suspensions inactivated by means of formaldehyde, and two to four weeks later a suspension of infectious virus was inoculated into the parotid duct. The gland was excised five or six days later, and the occurrence of antigen, and its quantity if present, as determined by complement fixation tests, were used as criteria of immunity or susceptibility. In about two-thirds of the vaccinated animals antigen was either not demonstrable by the method used or was present in quantities significantly less than in unvaccinated controls. The authors concluded that the procedure is capable of conferring a substantial degree of immunity, and this conclusion seems valid, since the infecting dose was a large one, not well adapted to demonstrate lesser degrees of resistance.

The work which has been briefly reviewed indicates that the complement fixation reaction may have diagnostic value in identifying atypical cases of mumps without salivary gland involvement, and occasionally in differentiating mumps from other conditions causing enlargement of these glands. The reaction seems to be as highly specific, but subject to the same limitations in its interpretation, as are serologic reactions in other infections.

The immediate practical value of this work depends chiefly upon the reliability of these measures as aids in the epidemiologic control of the disease. Manifestly it would be highly important to have means of distinguishing immune and susceptible individuals, and if possible of immunizing the latter. Since the immunity following recovery from mumps is usually of long duration and high in degree, proof that an individual had passed through an attack would be strong presumptive evidence of resistance. The animal experiments reviewed suggest that these measures may serve this purpose but definite conclusions can be drawn only from a study of human beings. Extensive studies along these lines have been undertaken, but at the time this review was written, only preliminary statements were available. In general a positive complement fixation reaction or intracutaneous test seems to be strong presumptive evidence of immunity, although a few individuals who had shown positive reactions proved susceptible on subsequent exposure to the virus. Conversely, a negative reaction constitutes presumptive evidence of susceptibility. Exceptions also occur, however, and hypersensitivity

may gradually disappear. It is not yet evident whether these exceptions are sufficiently frequent seriously to impair the practical value of the tests. Little can now be said regarding the immunization of human beings. The results obtained appear to be sufficiently encouraging to warrant the hope that an effective technic can be devised. One practical difficulty has been dependence on the parotid glands of monkeys as a source of virus. The other laboratory animals tested were insusceptible, and reported attempts to secure growth in tissue cultures and in developing chick embryos were unsuccessful. The final report of these studies will be of great interest.

## REVIEWS

*Penicillin Therapy Including Tyrothricin and Other Antibiotic Therapy* By JOHN A. KOLMER, M.D. 302 pages, 15 × 22 cm D Appleton-Century Co., New York 1945 Price, \$5.00

This timely monograph is offered primarily as a clinical guide to the rational use of penicillin and as such is of interest to the physician and dentist. However, Dr. Kolmer describes authoritatively the laboratory aspects of the source, production, detection, and assaying of penicillin, and also its physical, chemical, and pharmacological properties. The antimicrobial activity of penicillin *in vitro* and *in vivo* is discussed in detail.

The author has summarized the literature which has accumulated concerning administration and dosage of penicillin, principles of penicillin therapy, and therapeutic effectiveness of penicillin in the prevention and treatment of various diseases. He has carefully evaluated the abundant data on antibiotic therapy and has presented it in a stimulating and concise manner compatible with present data and experience but at the same time raising questions to be answered by further experiment and clinical trial.

The author has used the term "antibiotic" in a restricted sense to mean "antimicrobial agents produced by living bacteria, yeast, molds and other plants" and has included a chapter on tyrothricin, gramicidin S, streptothricin, patulin and chlorophyll.

Each chapter represents a review of a large number of articles, for example, the chapter on "Antimicrobial Activity of Penicillin" includes 95 references. Yet this work is more than a critical review, because the author goes beyond the present familiar substances and suggests the rôle of future therapeutic agents, such as streptomycin and penicillin-like antibiotics, in the treatment of disease.

The book is recommended to the clinician, bacteriologist, and biological chemist as a reference work on the nature of penicillin and a practical clinical guide to penicillin therapy.

M. V. P.

*Secretory Mechanisms of the Digestive Glands* By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C. Research Professor of Physiology, McGill University, Montreal, Canada, formerly Professor of Physiology, McGill University of Odessa, Russia and in Dalhousie University, Nova Scotia, Canada. 900 pages, 16 × 24 cm. Paul B. Hoeber, Inc., New York. Price, \$12.75.

The purpose of the author in presenting this volume is, according to the preface, to describe the mechanisms involved in the regulation of the secretory activity of the principal digestive organs under normal conditions and to serve as a physiological introduction to the pathology and the clinical investigation of the secretory apparatus of the alimentary tract. The book is based primarily upon the animal experiments of the author but includes the findings of other investigators in order to present as unified a picture as possible of the present knowledge of secretory mechanisms. The clinical application of some of the experimental work is discussed. The first few chapters present general principles correlating structure and function of the secretory cells of the gastrointestinal tract. Photomicrographs and schematic drawings serve to illustrate the changes which take place during secretory activity and during the restoration to the presecretory phase.

Following the more general chapters, specific phases of the secretory mechanisms of the various organs are presented in great detail. Sixteen chapters are devoted to gastric and six to salivary secretion. Four chapters are given over to the hormones

of the intestinal tract. Besides the well established hormones, there is a discussion of the possible hormone effect of substances such as lipocain and incretin.

The advantages of the somewhat complicated Agren-Lagerlof procedure for obtaining samples for gastric analysis and the use of histamine, insulin and the usual test meals as stimuli for gastric secretion are discussed in a chapter on clinical applications. The author has pointed out the advantages to be gained by the use of each of these stimuli.

This volume contains a wealth of material which is readily available through an extensive subject and author index.

Paul B Hoeber, Inc has maintained its usual high standards in the production of the volume.

M A A<sup>1</sup>

### BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Pulmonary Tuberculosis in the Adult Its Fundamental Aspects* By MAX PINNER, M D 579 pages, 23 × 15 cm 1945 Charles C Thomas, Springfield, Illinois Price, \$7.50

*Revista "Universidad de Antioquia"* No 70 339 pages, 24.5 × 17.5 cm April and May 1945 Universidad de Antioquia, Medellin-Colombia

*Carbon Monoxide Its Hazards and the Mechanism of Its Action* Public Health Bulletin No 290 257 pages, 23 × 15 cm 1944 Federal Security Agency—United States Public Health Service, Washington, D C

*Arquivos da Policia Civil de São Paulo* 658 pages, 28 × 19.5 cm December, 1944 Tip do Gabinete de Investigações, Rua dos Gusmoes, 300 São Paulo, Brasil

*Memoria de la Secretaria de Salubridad y Asistencia* 420 pages, 30 × 23.5 cm 1943-1944 Secretaria de Salubridad y Asistencia, Mexico, D F

## COLLEGE NEWS NOTES

### AND 'NOW THE FUTURE'

These News Notes are being gathered for the September number on V-J Day and uppermost in the minds of all of us is the FUTURE—our personal futures, the World future, the American future, the future of our institutions, the future, in particular, of the American College of Physicians

During the War the College waived dues and fees of its members serving in the armed forces aggregating upward of \$85,000 00, yet by careful management and inspired leadership it has successfully carried on and even increased many of its services. It has come through the war stronger than it entered. Classification of physicians for military duty, organization of the War-Time Graduate Medical Meetings for medical officers, conduct of regional meetings all over the United States so long as transportation facilities permitted, extension of the postgraduate course program are but a few of the activities of the College during the war. The journal, *Annals of Internal Medicine*, has been kept on a high plane, with little reduction in volume. The Executive Offices have functioned efficiently and effectively, with courtesy and service to all. There has been a steady though somewhat reduced growth in membership.

**AND NOW THE FUTURE** In June, 1945, the Board of Regents directed the further organization of its educational program under an educational director, working under the Regents and the Executive Secretary. It is hoped that by the time of publication of the September issue of this journal the educational director will have been appointed and ready to carry on. The program includes (1) Reestablishment of several Research Fellowships, (2) Resumption of annual award of the John Phillips Memorial Medal for research already accomplished, (3) Establishment of numerous Clinical Fellowships, (4) A marked extension of the postgraduate courses, especially to accommodate members returning from military service, (5) A service department to aid members retiring from military service to find residencies, assistantships and/or locations for work. The Executive Offices will welcome the suggestions and aid of its entire membership. A task worth doing must be well done.

Already the autumn program of postgraduate courses has been organized and announced. Just as soon as conditions permit, the great Annual Sessions and Regional Meetings of the College will be resumed—certainly the possibilities are promising for 1946.

"All for one and one for all," age worn though it may be, is an appropriate slogan as we work for the future.

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### A C P MEMBERS IN THE ARMED FORCES

Previously reported in these columns have been the names of 1,864 members of the American College of Physicians commissioned in the armed forces during the war. Of the new members elected during June, 1945, and published in the July number 56 are on military duty. These, added to the following newly reported admissions, bring the total to 1,923, 36% of the total members, Fellows and Associates, of the College.

#### Newly reported admissions

Seymour Jerome Gray, Chicago, Ill (Lieutenant MC, USNR)  
Myron David Miller, Columbus, Ohio (Surgeon USPHS)  
Walter C Nalty, Fort Bayard, N M (Lieutenant Colonel, MC, AUS)  
Edwin J Rose, Washington, D C (Colonel, MC, AUS)



### Retirements

Michael Bevilacqua, Woodhaven, L I, N Y  
 Pascal F Lucchesi, Philadelphia, Pa  
 James L McCartney, Garden City, N Y  
 William J Norfleet, Shreveport, La  
 William D Reid, Kezar Falls, Maine  
 Leonard G Rowntree, Philadelphia, Pa  
 Martin Van Buren Teem, Marietta, Ga

Some of these admissions and discharges are of a considerably passed date, but have only now been reported to the College. Members are urged to notify the Executive Offices, 4200 Pine St., Philadelphia 4, Pa., promptly of admissions or discharges, giving dates and changes of address.

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### CHANGES OF ADDRESS

Members and subscribers, especially those on military duty, frequently fail to re-ve the ANNALS OF INTERNAL MEDICINE owing to failure to register their changes of address. This situation has never been so acute as at present. The Medical Corps of the Army and Navy cannot, or do not, always furnish "directory service" for the forwarding of journals, often second class material is destroyed, and not returned to the publisher even though the mailing wrapper or envelope bears the inscription, "forwarding and return postage guaranteed." Owing to paper restrictions, publishers cannot guarantee replacement of undelivered journals. Physicians should promptly inform their societies and the publishers of journals to which they subscribe of address changes.

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### FUND GIVEN TO THE COLLEGE FOR ITS POST-WAR EDUCATIONAL PROGRAM

In the July issue of this journal the Post-war Educational Program of the American College of Physicians was announced. Under an Educational Director, the College proposes to expand very considerably its program of postgraduate courses, reestablish several research Fellowships, to award numerous clinical Fellowships, and to assist its members returning from military and naval service in locating residences, fellowships, locations for practice, etc.

Dr Willard O Thompson, F A C P, Chicago, Director of the American College of Physicians' course in internal medicine at Chicago institutions during October and November, 1944, has turned over a balance, from unexpended receipts, of \$713.30 to be added to the College funds for the promotion of its Post-war Educational Program. The College itself has appropriated to date a total of \$35,000 for this program. The College has the experience and the machinery to perform an effective and valuable service. The extent of that service may be limited only by the amount of funds available. It is hoped that additional funds will be contributed from other sources, including Foundations and the manufacturers of ethical drugs and other medical supplies. The College program proposes to be one of action and of service, not one of mere words.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College library of publications by members are gratefully acknowledged:

Colonel Julien E Benjamin, F A C P, Fort Devens, Mass.—1 reprint  
 Dr Nathan Blumberg, F A C P, Philadelphia, Pa.—1 reprint  
 Dr R H Felix, F A C P, Washington, D C.—1 reprint

Dr Arthur Grollman, F A C P, Dallas, Tex—19 reprints  
 Captain Byron Jay Hoffman (Associate), U S Army overseas—1 reprint  
 Dr E E Kattwinkel, F A C P, West Newton, Mass—1 reprint  
 Dr Louis I Kramer, F A C P, Providence, R I—1 reprint  
 Lieutenant Colonel Robert B Radl, F A C P, St Paul, Minn—1 reprint  
 Dr William S Reveno, F A C P, Detroit, Mich—2 reprints  
 Dr George X Schwemlein (Associate), Chicago, Ill—2 reprints  
 Lieutenant Commander Charles M Thompson (Associate), U S Navy overseas—2 reprints

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#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

Lieutenant Colonel Staige D Blackford, (MC), F A C P, of Charlottesville, Va, is now Chief of the Medical Service at Valley Forge General Hospital, Phoenixville, Pa. He succeeds Lieutenant Colonel Maurice A Schnitker, (MC), F A C P, of Toledo, O, who was given an overseas assignment. Colonel Blackford spent two and a half years overseas as Chief of the Medical Service of the 8th Evacuation Hospital in North Africa and Italy. He was awarded the Legion of Merit. Before entering the Army he was Associate Professor of Internal Medicine at the University of Virginia.

Major Edgar Stillwell Gordon, (MC), F A C P, Madison, Wis, has been promoted to Lieutenant Colonel.

Major General George F Lull, F A C P, Deputy Surgeon General, gave the keynote address on the occasion of the 170th anniversary of the Army Medical Department on July 27, 1945. After pointing out that today's Medical Department, more than one-half million strong, is gearing itself to new high standards in the care of American sick and wounded at home and abroad, he added, "We are justifiably proud of our World War II record of returning nearly ninety-seven of every hundred of our disabled soldiers to duty." General Lull spoke from Valley Forge, the birthplace of the Medical Department, founded by the Continental Congress upon the request of General George Washington.

Colonel John B Youmans, (MC), F A C P, Director of the Nutrition Division, recently visited various types of prisoner of war camps in the Ninth Service Command and made observations on dietary needs in relation to kind and amount of work performed. The operation of messes using mainly noncritical and ration-point-free items was studied and the effect of such dietaries on performance and response of prisoners was observed.

Centers for corneal transplant operations on suitable cases have been established at Valley Forge General and Dibble General Hospitals. Suitable cases will be sent to these centers.

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#### BARUCH COMMITTEE ON PHYSICAL MEDICINE

That the Baruch Committee on Physical Medicine, established in 1944 by Bernard M Baruch with a gift of \$1,190,000, is achieving wholly satisfactory results is made clear in its first annual report recently forwarded to the founder by Dr Frank H Krusen, F A C P, Director of the Committee.

In creating the Committee, Mr Baruch announced that its purpose would be to advance and encourage the knowledge and practice of physical medicine throughout the nation and the world with the special aim of bringing its benefits to disabled veterans of the war and of assisting in their rehabilitation and restoration to working health and usefulness.

The committee has defined physical medicine as follows: "Physical medicine is that branch of medical science which in conjunction with or succeeding surgery and

hospitalization, undertakes the long course of restoration to working activity by the employment of heat, light, water, electricity, massage, manipulation, exercise and mechanical devices" It is said that the committee's activities have caused increasing general interest in the field of medicine it fosters and growing cooperation and comprehension of it on the part of the public at large

The medical schools of ten universities and colleges, extending over the United States, are participating There is also a fellowship fund of \$100,000 for the encouragement of medical students at the various institutions who may plan to make physical medicine their specialty and to devote their professional careers to it Five fellowships have already been granted The grants to the different institutions have been as follows College of Physicians and Surgeons of Columbia University, \$400,000, New York University College of Medicine, \$250,000, Medical College of Virginia, \$250,000, Massachusetts Institute of Technology, \$50,000, University of Minnesota, \$40,000, University of Southern California, \$30,000, Harvard University, \$25,000, University of Iowa, \$15,000, Washington University of St Louis, \$10,000, University of Illinois, \$15,000, Marquette University, \$5,000 Harvard University received an additional special grant of \$30,000 with which to establish a three-year fellowship program The grant to Massachusetts Institute of Technology was made especially for the establishment of a laboratory for the training of Baruch fellows and other competent doctors interested in the field of physical medicine and for research and development in electronics in relation to the field

Approximately fifty scientific papers dealing with different phases of physical medicine have been prepared and distributed by committee members

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#### ARMY MEDICAL LIBRARY SEEKING COLLECTION OF PHOTOGRAPHS OF PROMINENT MEN IN AMERICAN MEDICINE

The Army Medical Library desires to obtain the cooperation of prominent Fellows of the American College of Physicians in building up its collection of portraits of persons prominent in the field of medicine As part of its program to expand this collection, it would appreciate receiving autographed photographs, preferably 8 x 10 inches in size, and unmounted, of each Fellow of the College Photographs should be plainly marked on the back with date and name of the subject and should be sent to The Director, Army Medical Library, 7th Street and Independence Avenue, S W, Washington 25, D C

The collection now includes some 10,000 photographs and prints of well known figures of the past 400 years It is intended that this collection shall be enlarged continuously by securing additional portraits of notable physicians of the past as well as those of contemporary worthies Each photograph will be catalogued and carefully preserved and made available for reproduction when required

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Colonel William P Holbrook, (MC), F A C P, Chief of Professional Services, Office of the Air Surgeon, has been assigned to assist the subcommittee of the Military Affairs Committee to carry on its investigation of alleged overstaffing of medical personnel in the Army under Senate Resolution 134 Senator Sheridan Downey, (D), of California, stated that Colonel Holbrook had been directed to assemble for the committee all possible statistics and data dealing with the subject and to have these and necessary supporting witnesses and recommendations ready for presentation to the Military Affairs Committee upon the reassembling of Congress in the autumn

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Major Michael Bevilacqua, (MC), F A C P, will revert to inactive status on October 2 He entered the Army on July 15, 1942, as a First Lieutenant; his first and only assignment was in the 10th Medical Laboratory, after training and two

tours of maneuvers, the unit went to Europe in February, 1944, and there was assigned to the First Army. It landed on Normandie Beachhead on D-11 and participated in the campaigns of Normandie, Northern France, Rhineland, Ardennes and Central Germany.

Major Bevilacqua was flown to the United States on July 14 and soon thereafter was notified of his release from active duty. He was awarded the Bronze Star Medal by General Hodges for meritorious service and his unit was awarded the Meritorious Service Unit Plaque for Superior Performance of Duty.

Colonel Henry Morgan Winans, (MC), F A C P, at present Chief of the Medical Service Brooke General Hospital, Fort Sam Houston, Texas, has recently received the honorary degree of Doctor of Laws from Baylor University.

Dr Victor F Cullen, F A C P, State Sanatorium, Md, has been made President-elect of the National Tuberculosis Association. Dr Cullen recently received the honorary degree of LL D from Mt St Mary's College, Emmitsburg, Md.

Dr Joseph T Roberts (Associate), Washington, D C, made the following recent addresses: (1) "Experiments on the Role of the Small Blood Vessels in Heart Failure, Coronary Artery Disease and Heart Pain" before the Washington Heart Association. (2) "Barbiturate Poisoning" before the Doctors' Hospital staff. (3) "Picrotoxin and Other Aspects of Barbiturate Poisoning" before the staff of Anderson Clinic.

Dr Herbert T Kelly, F A C P, Philadelphia, Pa, Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, addressed the Pennsylvania Chautauqua at Mount Gretna, Pennsylvania, on July 18, 1945, on "Food and Effects," followed by an illustrative film.

Lieutenant Colonel John W Shuman, (MC), F A C P, now attached to the Wadsworth General Hospital at West Los Angeles, California, has been awarded a silver plaque by the Hollywood Academy of Medicine for meritorious service as its President, 1937.

Colonel Shuman has been elected an honorary member of the American Geriatric Society.

Dr Hobart A Reimann, F A C P, Professor of Medicine at Jefferson Medical College, recently flew to Chungking with six other members of a medical commission to aid in combating the cholera epidemic in the Chinese capital. The commission consists of five doctors and two sanitary engineers and was organized by the United Nations Relief and Rehabilitation Administration at the request of the Chinese Government and Lieutenant General A C Wedemeyer, commanding U S forces in the Chinese theater. The Chungking epidemic began in June. By the middle of July when Dr Reimann left there were over 8,000 cases of cholera in the area of the Chinese capital.

Lieutenant Colonel Pascal F Lucchesi, (MC), (Associate), has been released from active duty and will resume his former work as Superintendent and Medical Director of the Philadelphia Hospital for Contagious Diseases.

Dr Harold Inman Goshline, F A C P, formerly of Ossining, N Y, is now Assistant Superintendent and Senior Psychiatrist to the New Mexico State Hospital at Las Vegas.

Dr. J C Geiger, F A C P, Director of Public Health, City and County of San Francisco, is the recipient of the decoration of the Orden de Vasco-Nunez de Balboa of the Republic of Panama, "for distinguished, distinctive and generous services in public health given over a long period of time to the residents from Panama and to Panama, and a living example of the perpetuation and enrichment of Pan-Americanism" This decoration is named for Vasco-Nunez de Balboa, the noted Spanish traveler, discoverer and historian who pointed out to the world and posterity that the Isthmus of Panama was the life-line of the American continents.

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#### COLONEL KEMP APPOINTED DEAN, WAYNE UNIVERSITY COLLEGE OF MEDICINE

Lt Col Hardy A Kemp, (MC), Secretary of the Army Medical School, Washington, D C, a graduate of St Louis University School of Medicine, 1926, and formerly Dean of Ohio State University College of Medicine, Columbus, has been appointed Dean of the Wayne University College of Medicine, Detroit

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Dr Harry J Perlberg, F A C P, Jersey City, has been elected President of the Radiological Society of New Jersey

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#### OHIO STATE UNIVERSITY COLLEGE OF MEDICINE ANNOUNCES GRADUATE TRAINING FOR VETERANS

Ohio State University College of Medicine recently announced a plan for post-graduate training, primarily for returning veterans and for interested physicians. Participants will be required to spend full time in the University Hospital or affiliated institutions of the Medical School for a period of not less than 2 weeks nor longer than 3 months, and will be under the direct supervision of a member of the faculty who will serve as a counselor.

For additional information, write Dr Bruce K Wiseman, F A C P, Kinsman Hall, Ohio State University College of Medicine, Columbus 10, Ohio

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Dr John O Piper, F A C P, of Waterville, Maine, has been chosen President-elect of the Maine Medical Association

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Dr Francis G Blake, F A C P, and Regent, A C P, was presented with the Charles V Chapin Memorial Award of the city of Providence for 1945. Dr Blake is Dean and Sterling Professor of Medicine at Yale University. He delivered the annual Chapin Oration before the local medical society on "Some Recent Advances in the Control of Infectious Diseases"

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Dr Ralph A Kinsella, F A C P, St Louis, has been appointed by Governor Donnelly to the Missouri State Board of Health for a 4-year term

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Dr Clarence H Beecher, F A C P, will relinquish his Acting Deanship and in the future devote his full time to the Professorship of Medicine at the University of Vermont College of Medicine. Dr William Eustus Brown, Associate Professor of Preventive Medicine at the University of Cincinnati College of Medicine, will be the full time Dean at the University of Vermont College of Medicine, effective September 1

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Dr Myron D Miller, F A C P, formerly of Columbus, Ohio, has entered the U S Public Health Service as a regular and permanent officer as of July 16 1945

## A C P POSTGRADUATE COURSES

On the inside back cover page of this issue will be found the complete schedule and announcement of the Postgraduate Courses offered by the American College of Physicians. Numerous advance reservations have been coming in regularly and members are urged to complete registration as far in advance as possible.

The detailed outlines of the courses, faculty personnel, and other announcements will appear in the Postgraduate Bulletin which will be sent automatically to all members of the College. Non-members can obtain copies of the Bulletin by writing to the Executive Offices, 4200 Pine St., Philadelphia 4, Pa.

At the time this notice is being prepared for press, directors of some of the courses have not yet sent in their full outlines, and hence they cannot be published in this issue. However, such outlines as are available follow.

## COURSE No 1—ALLERGY

(October 8-13, 1945)

*Roosevelt Hospital, New York, N Y*

ROBERT A. COOKE, M D, F A C P, *Director*

(Minimal Registration, 25, Maximal Registration, 50)

*Officers of Instruction*

Robert A. Cooke, M D, F A C P, Attending Physician and Director, Department of Allergy, Roosevelt Hospital

Horace S. Baldwin, M D, Assistant Professor of Clinical Medicine, Cornell University Medical College, Assistant Attending Physician and Chief of Allergy Clinic, New York Hospital

Otelia J. Bengtsson, M D, Clinical Assistant, Department of Allergy, Roosevelt Hospital

Lilian A. Boker, M D, Assistant Attending in Pediatrics and Clinical Assistant Department of Allergy, Roosevelt Hospital

Walter Brandes, M D, Pathologist, Roosevelt Hospital

Robert Chobot, M D, F A C P, Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University, Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital, Assistant Chief, Allergy Clinic, Roosevelt Hospital

Russell Clark Grove, M D, Associate Surgeon Otolaryngology, Roosevelt Hospital

Joseph Harkavy, M D, Associate in Medicine, Columbia University College of Physicians and Surgeons, Associate Physician and Chief of Allergy Clinic, Mt Sinai Hospital, Associate Physician, Montefiore Hospital

Selman Hebard, M D, Assistant Chief of Allergy Clinic, Roosevelt Hospital, Senior Clinical Assistant in Allergy, Outpatient Department, Mt Sinai Hospital

Foster Kennedy, M D, Professor of Neurology, Cornell University Medical College, Director, Neurological Department, Bellevue Hospital

Paul Klemperer, M D, Pathologist, Mt Sinai Hospital

Louis Schwartz, M D, Medical Director, Chief, Dermatoses Section, U S Public Health Service, Bureau of State Services, Bethesda Md

Will Cook Spain, M D, F A C P, Clinical Professor of Medicine, New York Post-Graduate School and Hospital, Columbia University, Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Medical School and Hospital

Albert Vander Veer, M D, Consultant in Allergy and Chief of Allergy Clinic, Roosevelt Hospital

Matthew Walzer, M D , Associate in Medicine, Cornell University Medical College, Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn

Although the course in Allergy will be given at the Roosevelt Hospital, the faculty consists of members of various medical schools and hospitals in New York and the U S Public Health Service All important phases of allergy will be covered in lectures and clinics on the theoretical and practical aspects of the subject

This year a special feature is made of colloquia on Friday afternoon and Saturday morning In this way small groups will be given an opportunity for free and informal discussion with various faculty members of assigned topics, and any subject not adequately covered in formal lectures may be brought up for consideration It is requested that registrants indicate their first, second and third choices, and assignments will be made as closely as possible with the expressed choices of the registrants

A reference list of desirable articles on allergy will be mailed to all registrants from the office of the American College of Physicians

### *Outline of Course*

*Monday, October 8*

A M Session

9 00-11 30 Registration

Fundamentals of Allergy and Allergic Disease

Dr Cooke

11 30- 1 00 Allergen Extracts Preparation and Standardization

Dr Spain

P M Session

2 00- 4 00 Skin Testing Methods and Interpretations

Dr Walzer

4 00- 6 00 Pathologic Anatomic Aspects of Allergic Disease

Dr Klemperer

*Tuesday, October 9*

### *Asthma*

A M Session

9 00-11 00 Infective Asthma

Dr Cooke

11 00- 1 00 Non-Infective Asthma

Dr Spain

P M Session

2 00- 4 00 Differential Diagnosis and Treatment of Status Asthmaticus

Dr Baldwin

4 00- 6 00 Pathology of Asthma

Dr Brandes

*Wednesday, October 10*

### *Allergic Rhinitis*

A M Session

9 00-11 00 Seasonal Type (1st session)

Dr Vander Veer

11 00- 1.00 Perennial Type

Dr Spain

P M Session

2 00- 3 30 Seasonal Type (2nd session)

Dr Vander Veer,

3 30- 4 30 Seasonal Hay Fever Special Problems

Dr Hebard

4 30- 6 00 Sinus Infection and Allergic Disease

Dr Grove

*Thursday, October 11*

## A M Session

- 9 00-10 00 Mold Allergy  
Dr Chobot
- 10 00-11 00 Pediatric Allergy  
Dr Chobot
- 11 00- 1 00 Industrial Dermatoses (Contact Dermatitis)  
Dr Schwartz

## P M Session

- 2 00- 4 00 Eczema Diagnosis, Specific and Symptomatic Therapy  
Dr Cooke
- 4 00- 6 00 Clinic  
Dr Cooke

*Friday, October 12*

## A M Session

- 9 00-11 00 Vascular Allergy, Meniere's Disease, Migraine  
Dr Harkavy
- 11 00- 1 00 Urticaria, Angioneurotic Edema and Gastrointestinal Allergy  
Dr Cooke

## P M Session

- 2 00- 4 00 Allergy and the Central Nervous System  
Dr Kennedy
- 4 00- 6 00 Colloquia
- I Skin Testing Gastrointestinal Allergy, Physical Allergy  
Dr Walzer
  - II Vascular Allergies Migraine, Meniere's Disease  
Dr Harkavy
  - III Asthma Allergic Rhinitis, Perennial  
Dr Spain
  - IV Allergic Rhinitis Seasonal, Mold Allergy  
Dr Vander Veer
  - V Allergic Dermatoses  
Dr Cooke

*Saturday, October 13*

## A M Session

- 9 00-12 00 Colloquia
- I Allergy Clinic
    - Allergy Clinic Set-up
    - Care of Syringes and Extracts
    - Practice in Skin Testing
    - Preparation of Extracts—Standardization
    - Care of Pollen
    - Passive Transfer Tests
    - Modification of Extracts
    - Drs Hebald, Boker and Bengtsson
  - 9 00-10 30 II Rhinological Examination and Diagnosis  
Dr Grove
  - III Pediatric Allergy—Mold Allergy  
Dr Chobot
  - IV Principles of Allergy Asthma  
Dr Cooke
  - V Allergic Rhinitis  
Dr Vander Veer



10 30-12 00

- VI Food Allergy Urticaria, Angio Edema  
Dr Chobot
- VII Vernal Catarrh Histamine—Hapamine  
Dr Cooke
- VIII Drug and Serum Allergy  
Dr Harkavy
- 

## COURSE No 2—INTERNAL MEDICINE

(October 15-27, 1945)

*University of Michigan Medical School and University Hospital  
Ann Arbor, Michigan*

CYRUS C STURGIS, M D, F A C P, *Director*

(Minimal Registration, 20, Maximal Registration, 50)

*Fees A C P Members, \$40 00, Non-members, \$80 00, Military Officers (active), Free*

*Officers of Instruction*

John Alexander, M A, Sc D, M D, F A C S, Professor of Surgery

Carl E Badgley, M D, F A C S, Professor of Surgery

Carl D Camp, M D, Professor of Neurology and Chairman of the Department

Frederick A Collier, M S, M D, F A C S, Professor of Surgery and Chairman of the Department

Arthur C Curtis, M D, F A C P, Professor of Dermatology

Albert C Furstenberg, M D, F A C S, Professor of Otolaryngology, Chairman of the Department and Dean of the Medical School

Fred J Hodges, M D, Professor of Roentgenology and Chairman of the Department

Norman F Miller, M D, F A C S, Professor of Obstetrics and Gynecology and Chairman of the Department

Reed M Nesbit, M D, F A C S, Professor of Surgery

Louis H Newburgh, M D, F A C P, Professor of Internal Medicine

Max M Peet, M D, F A C S, Professor of Surgery

Maurice H SeEVERS, M D, Professor of Pharmacology and Chairman of the Department

Cyrus C Sturgis, M D, F A C P, Professor of Internal Medicine and Chairman of the Department

Raymond W Waggoner, M D, Professor of Psychiatry and Chairman of the Department

Carl V Weller, M D, F A C P, Professor of Pathology and Chairman of the Department

Frank N Wilson, M D, F A C P, Professor of Internal Medicine

Paul S Barker, M D, Associate Professor of Internal Medicine

John B Barnwell, M D, Associate Professor of Internal Medicine

Frank H Bethell, M D, F A C P, Associate Professor of Internal Medicine and Assistant Director of Simpson Memorial Institute

Jerome Conn, M D, F A C P, Associate Professor of Medicine

Franklin D Johnston, M D, Associate Professor of Internal Medicine and Secretary of the Medical School

Richard H Lyons, M D, F A C P, Associate Professor of Internal Medicine

H Marvin Pollard, M D, F A C P, Associate Professor of Internal Medicine  
 John D Adcock, M D, F A C P, Assistant Professor of Internal Medicine  
 William D Robinson, M D, F A C P, Assistant Professor of Internal Medicine, in  
 charge of Rackham Arthritis Research  
 Francis F Rosenbaum, M D, Assistant Professor of Internal Medicine  
 Robert A Hettig, M D, Instructor in Internal Medicine  
 Daniel E Jenkins, M D, Instructor in Internal Medicine

This program is designed to give a survey of the recent developments in medicine  
 It consists of clinics, ward demonstrations and conferences, with ample opportunity  
 for discussion of the subjects presented

### *Outline of Course*

#### *Monday, October 15*

##### A M Session

8 00- 9 00 Registration Room 2040, University Hospital

9 00-11 00 Ward Rounds

Thyroid Diseases Section A 2NE

Dr Sturgis

Diabetes Section B 2NW

Dr Conn

11 00-12 00 Post-war Nutrition Problems

Dr Robinson

12 00-12 40 Motion Picture of Selected Medical Topics

##### P M Session

1 30- 2 30 Abuse of Rest in Surgery

Dr Coller

2 30- 3 30 Demonstrations

Section A Blood Transfusions

Section B Arthritis Unit

3 30- 5 00 Clinical Pharmacological Conference

Dr Sturgis, Dr Seevers and the Medical Staff

8 00 Smoker, Washtenaw Country Club

#### *Tuesday, October 16*

##### A M Session

9 00-11 00 Ward Rounds

Diabetes Section A

Dr Conn

Thyroid Diseases Section B

Dr Sturgis

11 00-12 00 Electrocardiographic Changes in Myocardial Infarction

Dr Wilson

12 00-12 40 Motion Picture of Selected Medical Topics

##### P M Session

1 30- 2 30 Surgical Treatment of Hypertension

Dr Peet

2 30- 3 30 Demonstrations

Section A Arthritis Unit

Section B Blood Transfusions

3 30- 5 00 Electrocardiographic Conference

Dr Wilson and the Medical Staff

*Wednesday, October 17*

## A M Session

9 00-11 00 Ward Rounds

Cardiac Failure Section A

Dr Lyons

Hypertension Section B

Dr Barker

11 00-12 00 Paroxysmal Rapid Heart Action

Dr Rosenbaum

12 00-12 40 Motion Picture of Selected Medical Topics

## P M Session

1 30- 2 30 Intra-thoracic Tumors

Dr Alexander

2 30- 3 30 Demonstrations

Section A Heart Station

Section B Tropical Medicine

3 30- 5 00 X-Ray Medical Conference

Dr Hodges, Dr Sturgis and the Medical Staff

*Thursday, October 18*

## A M Session

9 00-11 00 Ward Rounds

Hypertension Section A

Dr Barker

Cardiac Failure Section B

Dr Lyons

11 00-12 00 Kidney Function

Dr Newburgh

12 00-12 40 Motion Picture of Selected Medical Topics

## P M Session

1 30- 2 30 Tuberculosis of the Urinary Tract

Dr Nesbit

2 30- 3 30 Demonstrations

Section A Tropical Medicine

Section B Heart Station

3 30- 5 00 Medical Staff Conference

Dr Sturgis and the Medical Staff

*Friday, October 19*

## A M Session

9 00-11 00 Ward Rounds

Nephritis Section A

Dr Newburgh

Allergy Section B

Dr Jenkins

11 00-12 00 Spontaneous Hypoglycemia

Dr Conn

12 00-12 40 Motion Picture of Selected Medical Topics

## P M Session

1 30- 2 30 The Problem of the Positive Serological Test for Syphilis

Dr Curtis

2-30- 3 30 Demonstrations

Section A Allergy Clinic

Section B Gastroscopy

3-30- 5 00 Clinical Pathological Conference

Dr Williams and the Medical Staff

*Saturday, October 20*

## A M Session

- 9 00-11 00 Ward Rounds  
                   Allergy       Section A  
                   Dr Jenkins  
                   Nephritis   Section B  
                   Dr Newburgh  
 11 00-12 00 Disturbances of Leukopoiesis  
                   Dr Bethell

*Monday, October 22*

## A M Session

- 9 00-11 00 Ward Rounds  
                   Peptic Ulcer                               Section A  
                   Dr Pollard  
                   Subacute Bacterial Endocarditis   Section B  
                   Dr Barker  
 11 00-12 00 Some Disturbances in the Dynamics of the Circulation  
                   Dr Lyons  
 12 00-12 40 Motion Picture of Selected Medical Topics  
 P M Session  
 1 30- 2 30 Sinusitis  
                   Dr Furstenberg  
 2 30- 3 30 Demonstrations  
                   Section A   Simpson Institute  
                   Section B   Neuropsychiatric Institute  
 3 30- 5 00 Surgical-Medical Conference  
                   Dr Coller, Dr Sturgis and the Medical and Surgical Staffs

*Tuesday, October 23*

## A M Session

- 9 00-11 00 Ward Rounds  
                   Subacute Bacterial Endocarditis   Section A  
                   Dr Barker  
                   Peptic Ulcer                               Section B  
                   Dr Pollard  
 11 00-12 00 Tuberculosis the Minimal Lesion  
                   Dr Barnwell  
 12 00-12 40 Motion Picture of Selected Medical Topics  
 P M Session  
 1 30- 2 30 The Dysenteries  
                   Dr Pollard  
 2 30- 3 30 Demonstrations  
                   Section A   Neuropsychiatric Institute  
                   Section B   Simpson Institute  
 3 30- 5 00 Obstetrical-Medical Conference  
                   Dr Miller, Dr Sturgis and the Medical and Obstetrical Staffs

*Wednesday, October 24*

## A M Session

- 9 00-11 00 Ward Rounds  
                   Coronary Artery Disease   Section A  
                   Dr Johnston  
                   Liver Disease                               Section B  
                   Dr Pollard

- 11 00-12 00 Antibiotics  
Dr Adcock
- 12 00-12 40 Motion Picture of Selected Medical Topics
- P M Session
- 1 30- 2 30 Pain of Spinal Origin  
Dr Badgley
- 2 30- 3 30 Demonstrations  
Section A Diet Therapy  
Section B TB Unit
- 3 30- 5 00 X-Ray Medical Conference  
Dr Hodges, Dr Sturgis and the Medical Staff

*Thursday, October 25*

## A M Session

- 9 00-11 00 Ward Rounds  
Biliary and Liver Disease Section A  
Dr Pollard  
Coronary Artery Disease Section B  
Dr Johnston

- 11 00-12 00 Treatment of Anemia  
Dr Sturgis

- 12 00-12 40 Motion Picture of Selected Medical Topics

## P M Session

- 1 30- 2 30 Senescence  
Dr Camp
- 2 30- 3 30 Demonstrations  
Section A TB Unit  
Section B Diet Therapy
- 3 30- 5 00 Medical Staff Conference  
Dr Sturgis and the Medical Staff

*Friday, October 26*

## A M Session

- 9 00-11 00 Ward Rounds  
Obesity Section A  
Dr Newburgh  
Endocrinology Section B  
Dr Conn

- 11 00-12 00 Gastritis  
Dr Pollard

- 12 00-12 40 Motion Picture of Selected Medical Topics

## P M Session

- 1 30- 2 30 Modern Treatment of Syphilis  
Dr Curtis
- 2 30- 3 30 Demonstrations  
Section A Gastroscopy  
Section B Allergy Clinic
- 3 30- 5 00 Clinical Pathological Conference  
Dr Weller and the Medical Staff

*Saturday, October 27*

## A M Session

- 9 00-11 00 Ward Rounds  
Endocrinology Section A  
Dr Conn

Obesity                      Section B  
                                     Dr Newburgh  
 11 00-12 00   Question Period  
                                     Dr Sturgis and the Medical Staff   Room 2330

COURSE No 3—GENERAL MEDICINE

(October 29—November 3, 1945)

*University of Oregon Medical School, Portland, Ore*

HOMER P RUSH, M D, F A C P, *Director*

(Maximal Registration, 25)

*Officers of Instruction*

*Guests*

Major Ercell A Addington, MC Barnes General Hospital, Vancouver, Wash  
 Colonel Charles K Berle, MC, F A C P, Barnes General Hospital, Vancouver, Wash  
 Lieutenant Colonel Orlando B Mayer, MC, F A C P, Barnes General Hospital, Vancouver, Wash  
 Major Walter R Nickel MC, Barnes General Hospital Vancouver Wash  
 Major William W Waddell, MC, Barnes General Hospital, Vancouver, Wash  
 Colonel Irving S Wright, MC, F A C P, Medical Consultant, Ninth Service Command, Fort Douglas, Utah

*University of Oregon Medical School Faculty*

David W E Baird, M D, F A C P, Dean, Professor of Medicine  
 John H Benward, M D, Assistant Professor of Pediatrics  
 Joseph B Bilderback M D, Professor of Pediatrics, Head of Dept  
 T Homer Coffen, M D, F A C P, Clinical Professor of Medicine  
 Rudolph M Crommelin, M D, Clinical Instructor in Medicine  
 Joyle O Dahl, M D, Assistant Clinical Professor of Dermatology  
 Norman A David, M D Professor, Head of Dept of Pharmacology and Clinical Instructor in Medicine  
 Wesley E Gatewood, M D, Assistant Clinical Professor of Medicine.  
 Leon A Goldsmith, M D, F A C P, Assistant Clinical Professor of Medicine  
 Morton J Goodman, M D, Assistant Clinical Professor of Medicine  
 Hance F Haney M D, Professor of Physiology  
 Carl Heller, M D Clinical Instructor in Medicine  
 Blair Holcomb, M D F A C P Assistant Clinical Professor of Medicine  
 Charles N Holman, M D Medical Director of Hospitals  
 John J Krygier, M D Instructor in Medicine  
 John H Labadie M D Assistant Clinical Professor of Dermatology and Syphilology  
 Donald R Laird M D Assistant Clinical Professor of Surgery  
 Guy R McCutchan, M D, F A C P, Clinical Instructor in Medicine  
 Frank R Mount, M D F A C P, Assistant Clinical Professor of Medicine  
 Lawrence Noall, M D Associate Professor of Orthopedic Surgery  
 Edwin E Osgood, M D F A C P, Associate Professor of Medicine Head of the Division of Experimental Medicine  
 John Pierson M D, Resident in Medicine  
 Matthew C Riddle, M D Associate Professor of Medicine  
 Homer P Rush M D F A C P, Associate Professor of Medicine

Laurence Selling, M D, F A C P, Professor of Neurology, Head of the Division  
 James T. Speros, M D, Assistant Professor of Medicine  
 Marvin Schwartz, M D, Clinical Instructor in Medicine  
 Ben Vidgoff, M D, Clinical Instructor in Medicine  
 Charles P. Wilson, M D, Assistant Clinical Professor of Medicine

The purpose of this course is to review specific phases of medicine as it pertains to the Internist. This course will be given by members of the faculty with the help of members from the staff at Barnes General Hospital, and Colonel Irving S. Wright, Medical Consultant of the Ninth Service Command.

The program will be arranged to include lectures and informal discussions, round table meetings, and clinical conferences. It is hoped the class will take part in the latter both with questions and discussions.

The headquarters hotel will be the Heathman. All meetings will be held at the Medical School except for the round table discussions which will be held at the Heathman Hotel and the Tuesday afternoon meeting which will be given at Barnes General Hospital, Vancouver, Washington. It is hoped that those planning to come will make early hotel reservations. The program this year has been arranged to allow more time at noon, adequate time for transportation and shorter periods than last year's course.

### *Outline of Course*

#### *Monday, October 29*

A M Session—Medical School, Library

*Chairman* Dr. Rush

8 00– 9 00 Registration and Welcome

Drs. Baird, Selling and Rush

9 00– 9 40 Psychosomatic Medicine

Dr. Selling

9 40–10 20 Interpretation of Chest Signs

Dr. Osgood

10 20–10 30 Intermission

10 30–11 00 Anemias

Dr. Riddle

11 00–11 40 The Adrenal

Dr. Rush

11 40–12 30 Transportation Time

#### *Heathman Hotel*

12 30– 1 50 Round Table Discussion—Treatment of Syphilis

Drs. Dahl, Goodman and Labadie

1 50– 2 10 Transportation Time

P M Session—Medical School

*Chairman* Dr. Coffen

2 10– 3 30 Clinical Conference

Dr. Mount

3 30– 3 40 Intermission

3 40– 4 20 Myth of the Enlarged Heart

Dr. Coffen

4 20– 5 00 Rectal Diseases

Dr. Laird

#### *Tuesday, October 30*

A M Session—Medical School Library

*Chairman* Dr. Selling

- 9 00- 9 40 Psychosomatic Medicine  
Dr Selling  
9 40-10 20 Hepatitis \*  
Colonel Wright  
10 20-10 30 Intermission  
10 30-11 00 Anemias  
Dr Riddle  
11 00-11 40 The Adrenal  
Dr Heller  
11 40 Transportation Time

Afternoon Session at Barnes General Hospital arranged by Colonel Berle, Commanding Starting at 1 30 at the Red Cross Lecture Hall The following program is subject to change depending upon Army personnel  
*Chairman* Colonel Berle

- 1 30- 2 15 Lesions of the Oral Cavity as an Aid to Diagnosis  
Major Nickel  
2 15- 3 00 Clinical Observation in Intestinal Infections  
Major Waddell  
3 00- 3 45 Massive Doses of Penicillin in the Treatment of Bacterial Endocarditis  
Lieutenant Colonel Mayer  
3 45 Roentgenologist and Antral Gastritis  
Major Addington  
5 00 Tour of Hospital

*Wednesday, October 31*

A M Session—Medical School, Library  
*Chairman* Dr Riddle

- 9 00- 9 40 Headaches  
Dr Selling  
9 40-10 20 Peripheral Vascular Disease \*  
Colonel Wright  
10 20-10 30 Intermission  
10 30-11 00 White Blood Cell Diseases  
Dr Riddle  
11 00-11 40 The Adrenal  
Dr Heller  
11 40-12 30 Transportation Time

*Heathman Hotel*

- 12 30- 1 50 Round Table Discussion—Rheumatic Fever  
Drs Rush, Wright, Bilderback and Osgood  
1 50- 2 10 Transportation Time

P M Session—Medical School, Library  
*Chairman* Dr Goldsmith

- 2 10- 3 30 Clinical Conference  
Dr Selling  
3 30- 3 40 Intermission  
3 40- 4 20 Classification of Tuberculosis  
Dr Sperry  
4 20- 5 00 Medical Bone Diseases  
Dr Norill

\* Informal discussion with questions



*Thursday, November 1*

A M Session—Medical School, Library

*Chairman* Dr Holman

9 00- 9 40 Heart Tones

Dr Goodman

9 40-10 20 Unipolar Leads

Dr Schwartz

10 20-10 30 Intermission

10 30-11 00 White Blood Cell Diseases

Dr Riddle

11 00-11 40 The Adrenal

Dr Heller

11 40-12 30 Transportation Time

*Heathman Hotel*

12 30- 1 50 Round Table Discussion—Obesity

Drs Rush, Vidgoff, Heller and Crommelin

1 50- 2 10 Transportation Time

P M Session—Medical School

*Chairman* Dr Osgood

2 10- 3 30 Clinical Conference

Dr Osgood

3 30- 3 40 Intermission

3 40- 4 20 Classification of Tuberculosis

Dr Speros

4 20- 5 00 Medical Bone Diseases

Dr Noall

*Friday, November 2*

A M Session—Medical School, Library

*Chairman* Dr Goodman

9 00- 9 40 Heart Tones

Dr Goodman

9 40-10 20 Unipolar Leads

Dr Schwartz

10 20-10 30 Intermission

10 30-11 00 Hemorrhagic Diseases

Dr Riddle

11 00-11 40 The Adrenal

Dr Heller

11 40-12 30 Transportation Time

*Heathman Hotel*

12 30- 1 50 Round Table Discussion—Antibiotics

Drs Osgood, David and Benward

1 50- 2 10 Transportation Time

P M Session—Medical School

*Chairman* Dr McCutchan

2 10- 3 30 Clinical Conference

Dr Gatewood

3 30- 3 40 Intermission

3 40- 4 20 Cor Pulmonale

Dr Krygier

4 20- 5 00 Medical Bone Diseases

Dr Noall

*Saturday, November 3.*

A M Session—Medical School, Library

*Chairman* Dr Mount

9 00– 9 40 The Clinical Approach in the Care of the Chronic Patient

Dr Holcomb

9 40–10 20 Acid Ash Diet \*

Dr Wilson

10 20–10 30 Intermission

10 30–11 00 Coronary Disease

Dr Mount

11 00–11 40 Diabetes Insipidus

Dr Vidgoff

11 40 Some Observations on the Carotid Sinus Reflex

Drs Haney and Pierson

COURSE No 4—RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF  
CARDIOVASCULAR DISEASE

(November 5–10, 1945)

*Massachusetts General Hospital, Boston, Mass*

PAUL D WHITE, M D, F A C P, *Director*

(Minimal Registration, 30, Maximal Registration, 75)

*Fees A C P Members, \$20 00, Non-members, \$40 00, Military Officers (active), Free*

*Officers of Instruction*

Donald G Anderson, M D, Research Fellow in Medicine, Evans Memorial, Massachusetts Memorial Hospitals, Instructor in Medicine, Boston University School of Medicine

William B Bridges, M D, Commonwealth Research Fellow, Massachusetts General Hospital

C Sidney Burwell, M D, F A C P Physician, Peter Bent Brigham Hospital, Research Professor of Clinical Medicine and Dean, Harvard Medical School

Mandel E Cohen, M D, Junior Visiting Neurologist, Boston City Hospital, Instructor in Neurology, Harvard Medical School

Lewis Dexter, M D, Associate in Medicine, Peter Bent Brigham Hospital Associate in Medicine, Harvard Medical School

Robert E Gross, M D, F A C S Associate Visiting Surgeon Children's Hospital Associate in Surgery, Peter Bent Brigham Hospital Associate Professor of Surgery, Harvard Medical School

Barton E Hamilton M D, F A C P, Consultant in Cardiology Boston City Hospital and Boston Living-In Hospital, Instructor in Medicine, Courses for Graduates Harvard Medical School

T Duckett Jones M D, Research Director, House of the Good Samaritan, Assistant Physician, Massachusetts General Hospital, Associate Professor of Medicine, Harvard Medical School

Samuel A Levine, M D, F A C P, Physician, Peter Bent Brigham Hospital, Assistant Professor of Medicine Harvard Medical School

Robert R Linton M D, F A C S, Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery Harvard Medical School

\* Informal discussion with questions

Benedict Massell, M D, Research Associate, House of the Good Samaritan, Assistant in Medicine, Massachusetts General Hospital, Assistant in Medicine, Harvard Medical School

Maurice B Rappaport, E E, Chief Engineer, Electrophysiologic Research, Sanborn Company

Reginald H Smithwick, M D, F A C S, Associate Visiting Surgeon, Massachusetts General Hospital, Instructor in Surgery, Courses for Graduates, Harvard Medical School

Merrill C Sosman, M D, Radiologist, Peter Bent Brigham Hospital, Clinical Professor of Radiology, Harvard Medical School

Howard B Sprague, M D, F A C P, Associate Physician, Massachusetts General Hospital, Visiting Physician, House of the Good Samaritan, Instructor in Medicine, Courses for Graduates, Harvard Medical School

Richard H Sweet, M D, F A C S, Associate Visiting Surgeon, Massachusetts General Hospital, Instructor in Surgery, Harvard Medical School

Helen B Taussig, M D, Pediatrician, Johns Hopkins Hospital, Associate in Pediatrics, Johns Hopkins University School of Medicine

Edwin O Wheeler, M D, Graduate Assistant, Massachusetts General Hospital

Paul D White, M D, F A C P, Physician, Massachusetts General Hospital, Lecturer in Medicine, Harvard Medical School

Conger Williams, M D, Assistant in Medicine, Massachusetts General Hospital, Assistant in Medicine, Harvard Medical School

This course is designed to give in one week a summary of the recent advances and present status of our knowledge of cardiovascular disease with particular emphasis on clinical aspects. With some omissions of inadequate summaries of anatomy, physiology, pharmacology, etc, and with more emphasis on clinical advances, and with a faculty selected with great care, this course will be essentially a repetition of the course organized by Dr White for the College during the autumn of 1944.

*It is regretted that no additional registrations can now be accepted for this course because its capacity has already been exceeded from advance applications from members of the College whose registrations emanated from announcements previously appearing in the Annals of Internal Medicine*

### *Outline of Course*

#### *Monday, November 5*

#### A M Session—Out-Patient Lower Amphitheatre

9 00–10 00 Introductory remarks

Important clues in cardiovascular symptoms and signs, with particular emphasis on newer observations

Dr White

10 00–12 00 Auscultation with demonstration of phonocardiography and audible registration of heart sounds and murmurs

Dr Sprague and Mr Rappaport

12 00– 1 00 Advances in cardiovascular roentgenology

Dr Sosman

#### P M Session—Ether Dome

2 00– 3 00 Electrocardiography Its historical development and present place in clinical medicine

Dr White

3 00– 4 00 Recent advances in electrocardiography with particular reference to precordial leads

Dr Williams

- 4 00- 5 00 Blood flow, circulation time, ballistocardiography  
 Dr Cohen  
 Evening Session—Ether Dome  
 8 00-10 00 Test electrocardiograms  
 Dr White

*Tuesday, November 6*

- A M Session—Ether Dome  
 9 00- 1 00 Present status and recent advances in diagnosis and treatment of  
 congenital heart disease Clinic  
 Drs Gross, Taussig and White  
 P M Session—Ether Dome  
 2 00- 3 30 Subacute bacterial endocarditis Clinic Present status and recent  
 advances  
 Drs Anderson and Wheeler  
 3 30- 5 00 Neurocirculatory asthenia Clinic Present status and recent ad-  
 vances  
 Dr Cohen  
 Evening Session—Ether Dome  
 8 00-10 00 Test x-rays  
 Dr White

*Wednesday, November 7*

- A M Session—Ether Dome  
 9 00- 1 00 Rheumatic fever and rheumatic heart disease Clinic Recent  
 advances in diagnosis and treatment  
 Drs Jones and Massell  
 Afternoon and evening free

*Thursday, November 8*

- A M Session—Out-Patient Lower Amphitheatre  
 9 00- 1 00 Hypertension and hypertensive heart disease Clinic Recent ad-  
 vances in diagnosis and treatment  
 Drs Dexter, Bridges, Smithwick and White  
 P M Session—Ether Dome  
 2 00- 5 00 Coronary heart disease Clinic Recent advances in diagnosis and  
 treatment  
 Dr White and associates  
 Evening Session—Ether Dome  
 8 00-10 00 Test exercise in pathology  
 Dr White

*Friday, November 9*

- A M Session—Ether Dome  
 9 00- 1 00 Congestive heart failure Clinic Present status and recent ad-  
 vances  
 Drs White Williams and Bridges  
 P M Session—Ether Dome  
 2 00- 5 00 The Arrhythmias  
 Dr White and associates  
 Evening Session—Harvard Club  
 8 00-10 30 Round Table Conference  
 Drs Burwell Hamilton Levine and White

*Saturday, November 10*

A M Session—Ether Dome

9 00–11 00 Peripheral vascular disease Clinic Recent advances in diagnosis and treatment

Dr Linton

11 00–12 00 Pericarditis Clinic Recent advances in diagnosis and treatment

Drs Sweet and White

12 00– 1 00 The Cor Pulmonale

Dr White

Concluding Remarks

COURSE No 5—ENDOCRINOLOGY

(November 5–10, 1945)

*Chicago and Other Institutions*

*Hotel Continental*

*505 North Michigan Avenue*

*Chicago, Illinois*

WILLARD O THOMPSON, M D, F A C P, *Director*

(Minimal Registration, 50, Maximal Registration, 100)

*Fees A C P Members, \$20 00, Non-members, \$40 00, Military Officers (active), Free*

This course offers an opportunity for physicians to bring themselves up to date in the field of endocrinology. The faculty of fifty-two includes many of the most outstanding endocrinologists from all over the United States and Canada. Numerous institutions are represented, including

American College of Surgeons

American Medical Association

The Chicago Medical Society

Cleveland Clinic

Colorado State College

Columbia University

Cornell University Medical College

Duke University School of Medicine

Harvard Medical School

Johns Hopkins University

Marquette University School of Medicine

Mayo Foundation, University of Minnesota

The Medical Corps of the United States Army

Northwestern University Medical School

State University of Iowa College of Medicine

Tufts College Medical School

University of Chicago, The School of Medicine

University of Illinois College of Medicine

University of Oklahoma School of Medicine

University of Southern California

University of Toronto Faculty of Medicine

University of Utah School of Medicine  
 University of Wisconsin Medical School  
 Washington University School of Medicine

The physical arrangements for the course this year are ideal. The meetings will be held in the same hotel in which the men are living. An adequate number of guest rooms has been set aside and every effort will be made to contribute to the comfort of visiting physicians.

**Meeting Place** Hotel Continental, 505 North Michigan Avenue—this is within walking distance of the Loop. All meetings will be held in the Boulevard Room, fifth floor, except those on Saturday, November 10, which will be held in the Tally-Ho Room on the ninth floor. This day will be devoted to the regional meeting of the American College of Physicians for the states of Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin. This meeting is part of the Course and all physicians taking the Course whether they are members of the College or not are invited not only to participate in the scientific sessions of the regional meeting but also to attend the luncheon and the dinner.

**Luncheon** Tally-Ho Room, ninth floor, Hotel Continental, November 5, 6, 7, 8 and 9. **Boulevard Room**, fifth floor, November 10.

**Refreshments during intermissions** Gothic Room third floor, Hotel Continental, November 5, 6 and 7, Tropical Room, fifth floor, November 8 and 9.

#### *Officers of Instruction*

Raymond B. Allen, M.D., F.A.C.P., Dean, University of Illinois College of Medicine  
 William Allen, M.D., Professor of Gynecology and Obstetrics, Washington University School of Medicine, St. Louis

Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago, The School of Medicine

Eben Carey, M.D., Professor of Anatomy and Dean, Marquette University School of Medicine

Anton J. Carlson, LL.D., Ph.D., M.D., F.A.C.P., Professor of Physiology Emeritus, University of Chicago, The School of Medicine, and Rush Medical College

Warren Cole, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine

Arthur R. Colwell, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School

M. Edward Davis, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Chicago

V. L. Domm, M.D., Research Associate in Zoology, University of Chicago

Lester Dragstedt, M.D., F.A.C.P., Professor of Surgery, University of Chicago, The School of Medicine

Earl T. Engle, M.D., Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York

Frederick Falls, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Illinois College of Medicine

Ray Farquharson, M.D., Head of Department of Therapeutics, University of Toronto Faculty of Medicine, Consultant in Medicine to the R.C.A.F.

Morris Fishbein, M.D., Assistant Professor of Medicine, University of Illinois College of Medicine, Editor, Journal of the American Medical Association

Smith Freeman, M.D., Ph.D., Professor of Physiology, Northwestern University Medical School

F. X. Gassner, V.M.D., Associate Pathologist, Colorado Experimental Station, Colorado State College, Fort Collins, Colo.

- N C Gilbert, M D , F A C P , Professor of Medicine and Head of the Department, Northwestern University Medical School
- E C Hamblen, M D , F A C S , Associate Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Duke University School of Medicine, Chief of Endocrine Division and Endocrinologist, Duke Hospital, Durham, N C
- Carl G Hartman, Ph D , Professor and Head of the Department of Zoology and Physiology, University of Illinois, Urbana
- Norris J Heckel, M D , F A C S , Associate Professor of Urology (Rush), University of Illinois College of Medicine
- Don G Hildrup, M D , F A C S , Colonel, (MC), USA, Surgeon, Sixth Service Command, Chicago
- John Eager Howard, M D , Assistant Professor of Medicine, Johns Hopkins University School of Medicine, and Visiting Physician to the Johns Hopkins Hospital, Baltimore
- Charles Huggins, M D , Professor of Surgery (Genito-urinary), University of Chicago, The School of Medicine
- Ernest E Irons, M D , F A C P , Professor of Medicine, University of Illinois College of Medicine, Regent and President, American College of Physicians
- A C Ivy, M D , F A C P , Nathan Smith Davis Professor of Physiology, Northwestern University Medical School
- Victor Johnson, M D , Secretary, Council on Medical Education and Hospitals, American Medical Association
- Robert W Keeton, M D , F A C P , Professor of Medicine and Head of the Department, University of Illinois College of Medicine
- Edward C Kendall, M D , Professor of Biochemistry, Mayo Foundation, University of Minnesota, Rochester, Minn
- Allen T Kenyon, M D , Associate Professor of Medicine, University of Chicago, The School of Medicine
- Fred C Koch, Ph D , Professor of Biochemistry, Emeritus, University of Chicago
- Cyril M MacBryde, M D , F A C P , Assistant Professor of Clinical Medicine, Washington University School of Medicine, Director, Metabolism Division, Barnes Hospital, Director, Endocrine and Metabolic Clinics, Washington University Clinics, St Louis
- Malcolm T MacEachern, M D , F A C P , Assistant Professor of Medicine, Northwestern University Medical School, Director of Program of Hospital Administration and Associate Director, American College of Surgeons
- Joseph E Markee, Ph D , Professor of Anatomy, Duke University School of Medicine, Durham, N C
- E Perry McCullagh, M D , F A C P , Head of Endocrine Research Laboratory, Cleveland Clinic Foundation Hospital, Cleveland, Ohio
- Carl R Moore, Ph D , Professor and Head of the Department of Zoology, University of Chicago
- Josiah J Moore, M D , F A C P , Director, Moore Clinical Laboratory, Past President Chicago Medical Society
- Fred H Muller, M D , President, Chicago Medical Society
- Warren O Nelson, M D , Professor of Anatomy, State University of Iowa College of Medicine, Iowa City
- Rulon W Rayson, M D , Associate in Medicine, Harvard Medical School; Assistant in Medicine, Massachusetts General Hospital, Boston
- Henry T Ricketts, M D , Associate Professor of Medicine, University of Chicago, The School of Medicine
- Edward H Rynearson, M D , F A C P , Associate Professor of Medicine, Mayo Foundation, University of Minnesota, Rochester, Minn

- Lee T. Samuels, Ph D, Professor of Biochemistry, University of Utah School of Medicine, Salt Lake City
- Elmer L. Sevringhaus, M D, F A C P, Professor of Medicine, University of Wisconsin Medical School
- E. Kost Shelton, M D, D Sc, F A C P, Associate Professor of Medicine, University of Southern California, Los Angeles
- Ephraim Shorr, M D, Associate Professor of Medicine, Cornell University Medical College, Associate Attending Physician, The New York Hospital, New York
- LeRoy H. Sloan, M D, F A C P, Professor of Medicine, University of Illinois College of Medicine, Regent, American College of Physicians
- Samuel Soskin, M D, Ph D, Professorial Lecturer in Physiology, University of Chicago, The School of Medicine, Medical Director, Michael Reese Hospital
- Kenneth W. Thompson, M D, Managing Editor of the Journal of Clinical Endocrinology, Clinical Professor of Surgery, Tufts College Medical School, Boston
- Willard O. Thompson, M D, F A C P, Professor of Medicine (Rush), University of Illinois College of Medicine
- George W. Thorn, M D, F A C P, Heisey Professor of the Theory and Practice of Physic, Harvard Medical School, Physician-in-Chief, The Peter Bent Brigham Hospital, Boston
- Henry H. Turner, M D, F A C P, Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City
- George E. Wakerlin, M D, F A C P, Professor of Physiology and Head of the Department, University of Illinois College of Medicine, Associate Dean in charge of the Rush-Presbyterian Division of the University of Illinois College of Medicine

### *Outline of Course*

*Monday, November 5*

Anton J. Carlson, M D, F A C P, *Presiding*

A M Session—Boulevard Room fifth floor Hotel Continental

8 00– 9 00 Registration

9 00– 9 30 Present Status of Surgical Treatment of Toxic Goiter  
Dr. Cole

9 30–10 00 Management of Progressive Exophthalmos  
Dr. McCullagh

10 00–10 30 The Frequent Failure of Continued Thyroid Therapy to Maintain an Increased BMR or Inhibition of Thyroid Function by Prolonged Ingestion of Thyroid Substance  
Dr. Farquharson

10 30–10 45 Intermission—Refreshments, Gothic Room, third floor

10 45–11 15 Obesity An Endocrine Problem?  
Dr. Rynearson

11 15–11 45 Present Status of Thiouracil  
Dr. McCullagh

11 45–12 15 Addison's Disease  
Dr. Rynearson

12 15–12 45 Some Physiological Information Desirable in Treating Disorders of the Thyroid  
Dr. Rawson

12 45– 2 00 Luncheon—Tally-Ho Room, ninth floor  
Victor Johnson, M D, *Presiding*

P M Session—Boulevard Room, fifth floor

2 00– 2 30 Clinic Recent Advances in the Treatment of Toxic Goiter  
Dr. W. O. Thompson



- 2 30- 3 00 The Parathyroids, Calcium Metabolism and Osteoid Diseases  
Dr Freeman
- 3 00- 3 30 Modern Treatment of Parathyroid Tetany  
Dr MacBryde
- 3 30- 4 00 Present Status of Lipocair  
Dr Dragstedt
- 4 00- 4 15 Intermission—Refreshments, Gothic Room, third floor
- 4 15- 4 45 Endocrine Factors in Progressive Muscular Dystrophy  
Dr Carey
- 4 45- 5 15 Simmonds' Disease Severe Insufficiency of the Adenohypophysis  
—Pathological and Clinical Picture  
Dr Farquharson
- 5 15- 5 45 Thyroid Ovarian Relationships  
Dr Gassner

*Tuesday, November 6*

Ernest E. Irons, M D , F A C P , *Presiding*

A M Session—Boulevard Room, fifth floor

- 9 00- 9 30 Nutrition and Hormones  
Dr Samuels
- 9 30-10 00 Controversial Aspects of Diabetes Mellitus  
Dr Ricketts
- 10 00-10 30 The Treatment of Hypogonadism  
Dr W O Thompson
- 10 30-10 45 Intermission—Refreshments, Gothic Room, third floor  
Fred H. Muller, M D , *Presiding*
- 10 45-11 15 Anomalies of Fat Metabolism in Diabetes Which Lead to Cirrhosis  
of the Liver  
Dr Keeton
- 11 15-11 45 Improved Forms of Insulin  
Dr MacBryde
- 11 45-12 15 Diagnosis and Treatment of Diabetic Acidosis  
Dr Colwell
- 12 15-12 45 Relations of the Adrenal Cortex to Carbohydrate Metabolism and  
Work Capacity  
Dr MacBryde
- 12 45- 2 00 Luncheon—Tally-Ho Room, ninth floor  
Raymond B. Allen, M D , F A C P , *Presiding*

P M Session—Boulevard Room, fifth floor

- 2 00- 2 30 Islet Cell Tumors and the General Problem of Hypoglycemia  
Dr Howard
- 2 30- 3 00 Occlusion of External Pancreatic Secretion in Man Results as  
observed in late follow-up in patients with pancreatodu-  
denectomy for carcinoma of the head of the pancreas  
Dr Brunswick
- 3 00- 4 00 The Application of the Vaginal Smear Method to Clinical Endo-  
crinology  
Dr Shortt
- 4 00- 4 15 Intermission—Refreshments, Gothic Room, third floor
- 4 15- 4 45 Calcium Metabolism  
Dr Howard

- 4 45- 5 15 Hypometabolism and Hypothyroidism in Children (Cretinism, Childhood Hypothyroidism and Myxedema, Pituitary Tumor and Adiposogenital Dystrophy)

Dr McCullagh

- 5 15- 5 45 The Endocrines and Diabetes

Dr Soskin

*Wednesday, November 7*

N C Gilbert, M D, F A C P, *Presiding*

A M Session—Boulevard Room, fifth floor

- 9 00- 9 30 The Role of Hormones in Uterine Gland Formation

Dr Carl R Moore

- 9 30-10 00 Endocrine Regulation of Menstruation and Menstrual Irregularities

Dr Hamblen

- 10 00-10 30 Endocrine Basis of Spontaneous Abortion

Dr Falls

- 10 30-10 45 Intermission—Refreshments, Gothic Room, third floor

Josiah J Moore, M D, F A C P, *Presiding*

- 10 45-11 15 Disorders of Menstruation

Dr Engle

- 11 15-11 45 Gonadotropins in the Female

Dr Davis

- 11 45-12 15 Intersexuality

Dr Ivy

- 12 15-12 45 Functional Uterine Bleeding

Dr William Allen

- 12 45- 2 00 Luncheon—Tally-Ho Room, ninth floor

LeRoy H Sloan, M D, F A C P, *Presiding*

P M Session—Boulevard Room, fifth floor

- 2 00- 2 30 Adolescent Hypovarianism

Dr Hamblen

- 2 30- 3 00 Anabolic Effects of the Androgens

Dr Kenyon

- 3 00- 3 30 Morphological Basis for Menstrual Bleeding

Dr Markee

- 3 30- 4 00 Clinical Aspects of Endometrial Biopsy

Dr Hamblen

- 4 00- 4 15 Intermission—Refreshments, Gothic Room, third floor

- 4 15- 4 45 Treatment of the Menopausal Patient

Dr Engle

- 4 45- 5 15 Ovarian Development after Attempted Destruction of Cortex

Dr Carl R Moore

- 5 15- 5 45 Use of Sex Hormones in the Menopause

Dr William Allen

*Thursday, November 8*

Morris Fishbein, M D, *Presiding*

A M Session—Boulevard Room, fifth floor

- 9 00- 9 30 Hormonal Relationships of Breast Cancer

Dr Huggins

- 9 30-10 00 Hormonal Control of Testicular Function  
Dr Nelson
- 10 00-10 30 Endocrine Aspect of Prostatic Cancer  
Dr Huggins
- 10 30-10 45 Intermission—Refreshments, Tropical Room, fifth floor
- 10 45-11 15 Endocrine Regulation of Growth  
Dr W O Thompson
- 11 15-11 45 Hypoparathyroid Tetany  
Dr Sevringhaus
- 11 45-12 15 Significance of Gonadotropin Assays on Human Urine  
Dr Koch
- 12 15-12 45 The Management of the Obese Patient  
Dr Shelton
- 12 45- 2 00 Luncheon—Tally-Ho Room, ninth floor

Malcolm T MacEachern, M D , F A C P , *Presiding*

P M Session—Boulevard Room, fifth floor

- 2 00- 2 30 Eight Years of Clinical Experience with Testosterone Propionate  
Dr Turner
- 2 30- 3 00 Studies on Experimental Cryptorchidism  
Dr Nelson
- 3 00- 3 30 The Management of the Menopause  
Dr Shorr
- 3 30- 4 00 The Diagnosis and Management of Male Infertility  
Dr Heckel
- 4 00- 4 15 Intermission—Refreshments, Tropical Room, fifth floor
- 4 15- 4 45 Treatment of Sterility  
Dr Engle
- 4 45- 5 15 The Role of Hormones in Sexual Behavior  
Dr Domm
- 5 15- 5 45 Management of the Climacteric, Male or Female  
Dr Sevringhaus

*Friday, November 9*

George E Wakerlin, M D , F A C P , *Presiding*

A M Session—Boulevard Room, fifth floor

- 9 00- 9 30 Anorexia Nervosa  
Dr Keeton
- 9 30-10 00 Endocrine Therapy in Certain Urological Diseases  
Dr Heckel
- 10 00-10 30 Types of Endocrine Dwarfism  
Dr Kenyon
- 10 30-10 45 Intermission—Refreshments, Tropical Room, fifth floor
- 10 45-11 15 Endocrine Factors in Adolescence  
Dr Nelson
- 11 15-11 45 Thyrotoxic Myopathy  
Dr Thorn
- 11 45-12 15 Problems of Growth and Development  
Dr Shelton
- 12 15-12 45 Treatment of Addison's Disease  
Dr W O Thompson
- 12 45- 2 00 Luncheon—Tally-Ho Room ninth floor

Don G. Hildrup, Colonel, (MC), USA, *Presiding*

P M Session—Boulevard Room, fifth floor

2 00– 2 30 Diagnosis and Treatment of Adrenal Insufficiency  
Dr Thorn

2 30– 3 00 The Cushing Syndrome  
Dr Kenneth W Thompson

3 00– 3 30 The Significance of 17 Keto-Steroid and Other Steroid Excretion  
in Man  
Dr Koch

3 30– 4 00 Persistence of Estrogenic Effects  
Dr Turner

4 00– 4 15 Intermission—Refreshments, Tropical Room, fifth floor

4 15– 4 45 The Use and Abuse of the Dextrose Tolerance Test  
Dr Soskin

4 45– 5 15 The Influence of the Adrenal Cortex on the Metabolism of Sodium,  
Potassium and Chloride  
Dr Kendall

5 15– 5 45 Estrogen Assays, with Particular Reference to a New Test for  
Blood Estrogens  
Dr Hartman

*Saturday, November 10*

Joint Session of Postgraduate Course and Regional Meeting of the American College of Physicians

*Hotel Continental*

A M Session—Tally-Ho Room ninth floor

8 00– 9 00 Registration

9 00 Scientific Session, including the following papers  
Endocrine Causes of Sterility

Dr E C Hamblen

Endocrine Regulation of Menstruation

Dr Joseph Markee

Pregnancy Tests, Including a New Six-Hour Method in Which the  
Male Rat Testis Is Used as Indicator

Dr Carl G Hartman

Antihormones

Dr Kenneth W Thompson

Use of Concentrated Human Albumin in the Treatment of Edema  
of Renal and Hepatic Origin

Dr George W Thorn

Three or four non-endocrine papers to be announced later

1 00– 2 30 Luncheon—Boulevard Room fifth floor

P M Session—Tally-Ho Room, ninth floor

2 30 Continuation of scientific session of Regional Meeting of the  
American College of Physicians Program to be announced  
later

5 30– 6 30 Cocktails—Boulevard Room fifth floor

6 30 Dinner—Boulevard Room, fifth floor

## COURSE No 6—GASTRO-ENTEROLOGY

(November 12-17, 1945)

*School of Medicine of the University of Chicago**Dora De Lee Hall*Walter Lincoln Palmer, M D, F A C P, *Director*

(Minimal Registration, 20, Maximal Registration, 50)

Fee A C P Members, \$20 00, Non-Members, \$40 00, Medical Officers (active), Free

*Officers of Instruction*

William E Adams, M D, F A C S, Associate Professor of Surgery, University of Chicago

J Garrett Allen, M D, Instructor in Surgery, University of Chicago

Robert G Bloch, M D, F A C P, Professor of Medicine, University of Chicago

Alexander Brunschwig, M D, F A C S, Professor of Surgery, University of Chicago

Paul R Cannon, M D, Professor of Pathology, University of Chicago

Anton J Carlson, M D, F A C P, Professor Emeritus of Physiology, University of Chicago

Lt Col Earl R Denny, M D, F A C P, Chief of the Medical Service, Gardiner General Hospital, Chicago

Lilian Donaldson, M D, Instructor in Roentgenology, University of Chicago

Lester R Dragstedt, M D, F A C P, Professor of Surgery, University of Chicago

Jay M Garner, M D, F A C P, Instructor in Medicine, Northwestern University Medical School

Charles W Hock, M D, Assistant in Medicine, University of Chicago

Paul C Hodges, M D, Professor of Roentgenology, University of Chicago

Paul H Holinger, M D, Assistant Professor of Laryngology, Rhinology and Otology, University of Illinois

Eleanor M Humphreys, M D, Associate Professor of Pathology, University of Chicago

Andrew C Ivy, M D, F A C P, Professor of Physiology, Northwestern University

John R Lindsay, M D, Professor of Surgery (Otolaryngology), University of Chicago

Samuel N Maimon, M.D., Assistant in Medicine, University of Chicago

Jules H Masserman, M D, Assistant Professor of Psychiatry, University of Chicago

Walter L Palmer, M D, F A C P, Professor of Medicine, University of Chicago

Dallas B Phemister, M D, F A C S, Professor of Surgery, University of Chicago

Henry T Ricketts, M D, Associate Professor of Medicine, University of Chicago

William E Ricketts, M D, Assistant in Medicine, University of Chicago

Stephen Rothman, M D, Professor of Medicine (Dermatology), University of Chicago

Gerhart Schwarz, M D, Instructor in Roentgenology, University of Chicago

Major Paul L Shallenberger, M D, Gardiner General Hospital, Chicago

David Slight, M.D., Professor of Psychiatry, University of Chicago

Lowell D Snorf, M D, F A C P, Associate Professor of Medicine Northwestern University.

*Location* Dora De Lee Hall of the Chicago Lame-In Hospital, 5841 S Maryland Avenue, Chicago 37, Illinois*Lunches* May be obtained in the Cafeteria in the basement of the Billing Hospital across the street

*Hotel Accommodations* There are at least three first-class hotels located approximately one and one-half miles from the University. Each of these has promised to reserve some rooms for registrants in the Course. However, rooms should be reserved and the reservation confirmed by mail as soon as possible. In writing for reservations, please refer to the American College of Physicians.

The Windermere East Hotel at 1642 East 56th Street (Fairfax 6000) quotes single rooms at \$4 00 and \$5 00 per day and double rooms at \$6 00 and \$7 00.

The Del Prado Hotel at 5307 S. Hyde Park Boulevard (Hyde Park 9600) quotes single rooms at \$3 50, \$4 00 and \$5 00 per day and double rooms at \$5 00, \$6 00 and \$7 00.

The Shoreland Hotel at 5454 South Shore Drive (Plaza 1000) quotes single rooms at \$5 00 and \$6 00 and double rooms at \$7 00 and \$8 00.

#### *Outline of Course*

##### *Monday, November 12*

###### *A M Session*

- 8 30- 9 00 Registration Lying-In Library, Room 173, 5841 Maryland Avenue
- 9 00- 9 15 Assembly and Introductory Remarks  
Dr Palmer
- 9 15-10 00 The Hormones of the Digestive Tract  
Dr Ivy
- 10 00-10 40 Nervous Control of the Digestive Tract  
Dr Carlson
- 10 40-11 10 The Role of Amino-acids in the Ingestion of Food  
Dr Cannon
- 11 10-11 20 Intermission
- 11 20-12 00 Emotions and the Digestive Tract  
Dr Slight
- 12 00-12 30 Psychogenic Vomiting  
Dr Masserman
- 12 30- 1 00 Migraine and the Digestive Tract  
Dr Slight
- 1 00- 2 00 Lunch

###### *P M Session*

- 2 30- 3 30 Esophagoscopy (Moving Picture Demonstration)  
Dr Holinger
- 3 30- 3 50 Esophagitis  
Dr Cannon
- 3 50- 4 00 Intermission
- 4 00- 4 25 X-Ray Examination of the Esophagus  
Dr Schwarz
- 4 25- 4 45 Esophageal Varices  
Dr Lindsay
- 4 45- 5 30 Benign Stricture of the Esophagus  
Dr Palmer

##### *Tuesday, November 13*

###### *A M Session*

- 9 00- 9 30 Scleroderma and Esophageal Stricture  
Dr Rothman and Lindsay
- 9 30-10 00 Morphology of Esophageal Carcinoma  
Dr Humphreys
- 10 00-10 30 Surgical Treatment of Esophageal Carcinoma  
Dr Adams

- 10 30-10 50 Radiation Therapy of Esophageal Carcinoma  
Dr Hock
- 10 50-11 00 Intermission
- 11 00-11 30 Surgical Treatment of Benign Lesions of the Esophagus  
Dr Adams
- 11 30- 1 00 Cardiospasm, with case demonstrations  
Dr Palmer
- 1 00- 2 00 Lunch
- P M Session
- 2 00- 2 30 Gastric Analysis  
Dr. Palmer
- 2 30-2 50 The Technique of the Gastro-duodenal X-Ray Examination  
Dr Hodges
- 2 50- 3 30 Gastroscoy and Gastritis  
Dr Maimon
- 3 30- 4 00 An Evaluation of Gastroscoy and X-Ray  
Dr William E Ricketts
- 4 00- 4 10 Intermission
- 4 10- 4 40 Tumor Forming Gastritis  
Dr Maimon
- 4 40- 5 00 Gastritis and Dyspepsia  
Dr Palmer

*Wednesday, November 14*

A M Session—PEPTIC ULCER

- 9 00-10 00 Pathogenesis and Pain Mechanism  
Dr Palmer
- 10 00-10 30 X-Ray Manifestations  
Dr Donaldson
- 10 30-11 20 Medical Treatment  
Dr Palmer
- 11 20-11 30 Intermission
- 11 30-12 15 Surgical Treatment  
Dr Dragstedt
- 12.15- 1 00 Treatment of the Complications  
Dr Palmer

1 00- 2 00 Lunch

P M Session

- 2 00- 3 00 Pathogenesis of Gastric Cancer  
Dr Palmer
- 3 00- 3 20 X-Ray Manifestations  
Dr Hodges
- 3.20- 3 45 Gastroscoyic Aspects  
Dr William E Ricketts
- 3.45- 3 55 Intermission
- 3 55- 4 30 The Life History of Gastric Cancer  
Dr. Palmer
- 4 30- 5 30 Surgical Treatment of Gastric Cancer  
Dr Brunschwig

*Thursday, November 15*

A M Session

- 9 00- 9 30 The Results of Surgical Treatment of Gastric Cancer  
Dr. Maimon
- 9 30-10 00 Peptic Dyspepsia and Gastric Motility  
Dr. Palmer

- 10 00-10 50 Physiology of the Liver  
Dr Ivy
- 10 50-11 00 Intermission
- 11 00-11 30 Liver in Relation to Serum Protein Formation  
Dr Humphreys
- 11 30-12 00 Hepatic Function Tests  
Dr Allen
- 12 00-12 40 Infectious Hepatitis  
Major Shallenberger
- 12 40- 1 00 Toxic Hepatitis  
Dr Palmer
- 1 00- 2 00 Lunch
- P M Session
- 2 00- 2 30 Cholelithiasis  
Dr Phemister
- 2 30- 3 00 Gall Bladder Dyspepsia  
Dr Palmer
- 3 00-3 40 Surgery of the Pancreas, Liver, and Biliary Ducts  
Dr Brunswick
- 3 40- 3 50 Intermission
- 3 50- 4 15 The Effect of Total Pancreatectomy on Diabetes Mellitus  
Dr Henry T Ricketts
- 4 15-4 35 Luetic Hepatitis and Splenomegaly (Case Presentation)  
Dr Rothman
- 4 35- 5 30 Pathology Conference, Hepatic Cirrhosis  
Drs Humphreys and Palmer

*Friday, November 16*

A M Session

- 9 00- 9 20 The X-Ray Diagnosis of Small Intestinal Lesions  
Dr Hodges
- 9 20-10 45 Regional Enteritis with case presentations  
Drs Dragstedt, Palmer and Hock
- 10 45-11 15 Tuberculous Enteritis  
Dr Bloch
- 11 15-11 25 Intermission
- 11 25-11 50 Bacillary and Salmonella Infections  
Major Shallenberger
- 11 50-12 35 Amebiasis  
Lt Col Denny
- 12 35- 1 00 Acute Enteritis  
Dr Palmer
- 1 00- 2 00 Lunch

P M Session

- 2 00- 3 00 Non-specific Ulcerative Colitis, Clinical Picture (Motion Picture Demonstration)  
Dr Snorf
- 3 00- 3 30 Complications  
Dr William E. Ricketts
- 3 30- 3 40 Intermission
- 3 40- 4 30 Case Presentations  
Drs Dragstedt, Palmer and William E. Ricketts
- 4 30- 5 30 Proctoscopic Cinematography  
Dr Garner



*Saturday, November 17*

A M Session

- 9 00- 9 50 Steatorrhea Case Presentations  
Dr Henry T Ricketts
- 9 50-10 20 Treatment of Peritonitis Complicating Ulcerative Colitis  
Dr William E Ricketts
- 10 20-10 50 Radiation Injuries of the Intestine  
Dr Hock
- 10 50-11 00 Intermission
- 11 00-11 45 Carcinoma of the Colon  
Dr Phemister
- 11 45-12 15 Pruritus Ani  
Dr Rothman
- 12 15- 1 00 Constipation, Diarrhea, and the Irritable Colon  
Dr Palmer
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WAR-TIME GRADUATE MEDICAL MEETINGS

With the conclusion of the war it is anticipated that the operations of the Committee on War-Time Graduate Medical Meetings will soon terminate. It is proposed, however, to complete all present scheduled programs.

A really fine service to the medical officers in the armed forces has been carried on to a fruitful end. The Central Committee, consisting of Dr F F Borzell, F A C P, Chairman and representative of the American Medical Association, Dr George Morris Piersol, F A C P, representative of the American College of Physicians, and Dr Alfred Blalock, F A C S, representative of the American College of Surgeons, deserves the congratulations and appreciation of the medical profession as a whole and of those in the armed services in particular. Thousands of programs covering all the main divisions of medicine and surgery, have been carried on at army and navy installations. Under the original chairmanship of Captain Edward L Boitz, (MC) U S N R, an efficient nationwide organization was effected. The various zone committees and chairmen and the many members of the faculty who have given of their thought and time are entitled to the plaudits of all.

An extensive two-day program was carried on September 14-15 at the DeWitt General Hospital at Auburn, California. It is not herein published because the meeting has already been concluded.

Other programs scheduled and yet to be given follow:

Region No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

October 5—Results of Penicillin Therapy of Syphilis in the European Theater—Colonel Donald M Pillsbury

October 26—Recent Advance in the Treatment of Acute Intestinal Obstruction—Dr I L Eliason or Dr Robert Welty

Region No 21 (Southern California)—Lt Comdr G C Griffith, Chairman, Capt H P Schenck, Dr J F Churchill, Dr W A Morrison, Maj N Nixon

*Birmingham General Hospital, San Anis, California*

September 26—Cardiovascular Problem—Dr W Gordon Gurnett

*Station Hospital, Camp Cooke, Camp, California*

September 10—War Wound of the Chest—Lieutenant Commander J P O'Connor and Lieutenant Henry Jaffe

*U S Naval Hospital, Naval Air Station, Alameda, California*

September 18—The Use of Fibrin and Fibrinolysin in Wound Healing—Captain Harry P. Schenck

*A A F Regional and Convalescent Hospital, Santa Ana, California*

September 18—Rheumatic Heart Disease—Dr. Louis E. Martin

*Hoff General Hospital, Santa Barbara, California*

September 19—War Wounds of the Chest—Lieutenant Commander J. P. O'Connor and Lieutenant Henry Jaffee

*Torney General Hospital, Palm Springs, California*

September 18—The Management of the Simple Skin Diseases—Lieutenant Colonel Everett R. Seale

*U S Naval Hospital, Santa Margarita Ranch, Occidental, California*

September 27—Differentiation Between the Protozoal and Bacillary Dysenteries—Dr. John F. Kessel

*U S Naval Air Training Station, San Diego, California*

September 21—The Malingering Tests—Dr. John Mackenzie Brown and Mr. Raymond Brown

*U S Naval Hospital, Long Beach, California*

September 19—Problems in Tuberculosis—Commander W. L. Rogers

*U S Naval Hospital, Corona, California*

September 27—The Rh Factor—Captain George Macer

Merck and Co., Inc., have announced that construction of large manufacturing facilities is being started for the production of streptomycin, a new antibiotic. A production unit consisting of three buildings, including several large fermenters and with 60,000 sq. ft. of floor space, will be constructed at the company's Stonewall Plant at Elkton, Va. A unit for drying and packaging the drug, with 30,000 sq. ft. of floor space, will be constructed at the company's main plant at Rahway, N. J. Total cost will approximate \$3,500,000. The new plant is expected to go into production early in 1946.

For many months, Merck has supplied military and other doctors with streptomycin for experimental purposes, from its pilot plant. Clinical study of the many possible uses of streptomycin will be continued as more material becomes available.

Extracted from a mold in much the same manner as penicillin is obtained, streptomycin has activity against certain bacteria which are unaffected by penicillin. In this class are bacteria which cause serious infections of the urinary tract, certain intestinal ailments, and wound infections. Streptomycin already is considered the best known drug for the treatment of tularemia. It has proved highly effective in the treatment of influenzal meningitis, infections due to the Salmonella group, and cystitis caused predominantly by gram-negative organisms. Experiments lead to the hope that it will be useful in the treatment of other diseases including undulant fever and possibly even tuberculosis.

#### DDT "BUG BOMBS" WAR ON PACIFIC INSECTS

DDT-filled Bug Bombs, produced at the rate of more than 1,300,000 a month by Westinghouse alone, are now helping Yanks fight the insect enemy in the Pacific. It was announced by J. H. Ashbaugh, Vice President in charge of the Electric Appliance Division of the Westinghouse Electric Corporation. The bombs are produced

at both the Mansfield and East Springfield, Mass., plants of the Company, as well as by other manufacturers

The Bug Bomb, an insecticide dispenser, is a pint-sized, throw-away container made of light-weight steel from which an aerosol—or mist—is discharged through a valve. The aerosol, using Freon gas as its propellant, now contains DDT.

The entire supply of these "bug bombs" goes to the United States Army for use in planes and ships, and in insect-infested land installations.

Until the recent change-over to DDT, more than 22,000,000 "bombs," containing pyrethrum and sesame oil as the insecticide, had been produced by Westinghouse. In use, however, they were restricted to eradication of malaria-carrying mosquitoes, owing to the limited supply of pyrethrum available. The principal pre-war source of pyrethrum was Japan, although some is grown in other parts of the world.

The Army wanted to permit use of the aerosol "bombs" against such pestiferous and dangerous bugs as flies and lice, and as the pyrethrum supply was not sufficient to permit increasing this ingredient to properly control such insects, DDT, the newly discovered insecticide, was added.

"Now both insect poisons—DDT and pyrethrum—are included in the formula because a combination is more effective against a larger variety of insects than either by itself," Mr. Ashbaugh said.

Some peculiar properties of DDT made it impossible to add it to the old formula without taking these "quirks" into account, Mr. Ashbaugh pointed out. DDT is a powder made with synthetic materials, and is not soluble in water.

The problem in using it in a bomb was to transform it into a liquid, he continued. Therefore, hydrocarbon oil, in which it is soluble, was added to the formula. The oil also helps make the insecticide stick to the insect. Another chemical, cyclohexanone, also helps to dissolve the DDT.

Actually the formula now used in the insecticide contains only about 3 per cent DDT, and approximately 2 per cent pyrethrum, while 85 per cent of it is Freon, the dispensing agent. All of the ingredients—DDT, cyclohexanone, pyrethrum, hydrocarbon oil and Freon—must be controlled rigidly as to quality, weight and volume.

"Cyclohexanone is also 'tricky' to handle because it readily absorbs moisture from the air," Mr. Ashbaugh said. "This makes it necessary to process it by distillation to remove some of this water. It is then pumped into an automatic weighing hopper as is the DDT, and dumped into a mixing tank. Hydrocarbon oil is added after it also is carefully weighed."

The ingredients are automatically mixed until they are completely dissolved and then are placed in storage tanks for use. Before the solution is actually put into the bombs, however, it is weighed once more in small batches and mixed with pyrethrum extract, which—at about \$10 a pound—is the most expensive of the components. The final step is to mix Freon with the other ingredients and the resulting liquid is ready to go into the Bug Bomb.

This insecticidal solution is discharged into the air, where the Freon evaporates. The resulting aerosol is a suspension in the air of tiny particles of highly concentrated insecticide.

Entomologists believe that DDT kills insects in two ways: sometimes it acts internally, being taken into the system during feeding, or it can act as a contact poison which is absorbed by the insect, killing it by paralyzing its nerves. Some insects are affected by DDT in both ways.

*OBITUARIES*

## DR ARTHUR WEAVER WHITE

Dr Arthur Weaver White was born June 3, 1877, in Paxton, Illinois, the son of Weaver and Ariabella White. He died June 11, 1945.

He received an A B degree from Monmouth College, Illinois in 1898 and an A M in 1907. He graduated from Rush Medical College in 1902 and studied in Europe in 1910.

He married Miss Winifred Bushnell on April 29, 1903, who now survives him. His only child, Sherrill Weaver White, is in active service as a Captain in the U S M C.

Dr White began his active medical career in Oklahoma City in 1905 in the general practice of medicine. He was one of the founders of the Epworth Medical School, which was later taken over by the University of Oklahoma. At the time of his death he was Clinical Professor of Medicine and had had an active teaching career. He was made Emeritus Professor of Medicine in the University on July 1, 1944, but because of the exigencies of war and the absence of so many younger men, he continued his teaching.

He was certified by the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1920, member, Oklahoma City Academy of Medicine, Oklahoma City Internists Association, Honorary member of Pi Beta Pi Medical Fraternity, County, State and American Medical Association. He was on the staff of St Anthony's Hospital, and Chairman of the Internes Committee.

He was active in his profession up to the day of his death, and had even started to his office when he came back home, and died suddenly of a coronary occlusion.

He was a member of the Men's Dinner Club, Chamber of Commerce, Presbyterian Church, Saddle Club, and was very civic minded. His hobbies were hunting, fishing and horseback riding. He had served as a Captain M C, in world War I. He was urbane, meticulous in his profession and his personal appearance.

He was the author of many papers on diseases of the stomach and intestines. He gave most of his attention to his specialty, and was generous of his time and talents on behalf of organized medicine, appearing on many programs in city, state and national gatherings. He drew patients from a vast area, enjoyed a large practice, and was well loved both by his confreres and those in the community in general, and his absence will create a big void.

LRA A. RIELY, M D, F A C P

Governor for Oklahoma

## DR. FREDERICK B. MINER

Dr. Frederick Bingham Miner, Fellow of the American College of Physicians since 1924, was born in Bridport, Vermont in 1876, and died at his home in Flint, Michigan, on April 26, 1945.

Following his preparatory training, Dr. Miner took up the study of medicine at the University of Michigan where he remained for two years, then entered the Detroit College of Medicine and Surgery where he received his degree of Doctor of Medicine in 1906.

Deeply interested in neuropsychiatry, Dr. Miner served as a member of the staff of Oak Grove Hospital in Flint, which was under the direction of the late Dr. C. W. Burr, returning to general practice for the next eight years.

When World War I began, Dr. Miner was commissioned into the United States Army and served as a captain from September, 1918 until June, 1919. Upon discharge from the army, he resumed private practice in Flint, Michigan, specializing in pediatrics.

In the year 1921 Dr. Miner was appointed chairman of the committee on endemic goiter of the American Public Health Association, after he advocated the use of iodized salt in the prevention of goiter.

For many years Dr. Miner was a member of the Medical Advisory Board at Women's Hospital, Chief of Pediatric Staff at St. Joseph's Hospital, a member of the General Staff at Hurley Hospital, and Attending Physician at King's Daughters' Foundling Home. He was a Diplomat of the American Board of Pediatrics, Fellow of the American Academy of Pediatrics, a member of the Genesee County and Michigan State Medical Societies, the American Medical Association, and the American Public Health Association.

In addition to his keen interest in medicine, Dr. Miner was a lover of flowers, and he was a trustee and former vice president of the Michigan State Horticultural Society.

The Michigan Fellows and Associates of the American College of Physicians record with deep regret the death of Dr. Miner, a noble and scholarly gentleman, who gave so much to the public service and gave to the practice of Medicine much dignity. His place in the profession will not be easily filled as he leaves many close friends and faithful patients.

Dr. Miner is survived by his wife, Mrs. Katharine Miner, a daughter, Mrs. H. Donald Selter, and a son, Frederick, now serving in the United States Navy.

P. I. EDWARDS, M.D., F.A.C.P.,  
Acting Governor for the State of Michigan

## DR. ROBERT McNAIR PURDIE

On April 9, 1945, Dr. Robert McNair Purdie, F.A.C.P., of Houston, Texas, died of a subarachnoid hemorrhage. Dr. Purdie was born in

Pocatello, Idaho, on July 4, 1898. His pre-medical training was received at the University of Utah, Salt Lake City, and he attended Northwestern University Medical School in Chicago, Illinois, graduating in 1922. After an internship at Cook County Hospital, he came to Houston, Texas, in 1924, where he devoted his entire time to the practice of Internal Medicine. In 1938 Dr. Purdie was elected a Fellow of the American College of Physicians.

Dr. Purdie was on the Staff of all the hospitals in Houston, taking an active part in all medical affairs. He served as Secretary and later as Vice-President of the Harris County Medical Society. His early death, coming at the height of his medical career, left a host of friends and patients to mourn his passing. He is survived by his wife, a daughter Patricia, and two sons, Robert and Burke, all of Houston.

M. D. LEVY, M. D., F. A. C. P.,  
Governor for Texas

#### DR. JESSE HEADEN INMAN

Jesse Headen Inman, an Associate of the College since 1941, died at his home in Bakersfield, California, July 15, 1945, of carcinoma of the colon.

Dr. Inman was born November 25, 1901. He received his A. B. from the University of California in 1925 and his M. D. from the same institution in 1929. He served a residency at the University of Michigan, 1929-30. He was Resident Physician of the Sutter Hospital, Sacramento, 1930-31, Resident Pathologist at the Pennsylvania Hospital, Philadelphia, 1931-32, and Pathologist, Kern General Hospital, 1933-36, since 1938, Pathologist for Mercy Hospital, Bakersfield.

In 1940, Dr. Inman was Vice President of the Kern County Medical Society. He was a member of the California State Medical Society, the California Heart Association, and the American Society of Clinical Pathologists.

The loss of Dr. Inman will be keenly felt by the profession in Bakersfield and vicinity.

ROY E. THOMAS, M. D., F. A. C. P.,  
Governor for Southern California

#### DR. JOHN PASCAL SAWYER

Dr. John Pascal Sawyer, F. A. C. P., Emeritus Professor of Clinical Medicine in Western Reserve Medical School, died June 17, 1945, at the age of 83 years. He had been a member of the faculty of the Medical School for 44 years, beginning as a pioneer in the use of the microscope in medical teaching. He was said to have given the first course in laboratory physiology west of the Alleghenies.

Dr. Sawyer, son of a physician, grew up in Cleveland, graduated from Western Reserve's Adelbert College in 1883 and from the Medical Depart-

ment in 1886. Then followed two years of study abroad, especially in physiology in Berlin and Freiburg. He returned as an enthusiastic young teacher and took a leading part in applying the newer scientific methods at Western Reserve Medical School. His clinical interests centered largely around the field of gastro-enterology. He was interested in the organization of the American Gastro-enterological Association, a member in 1900, and its president in 1907. For many years, Dr. Sawyer was known as a leader in this field, which he often referred to as "the most neglected part of medicine and yet the one presenting the greatest therapeutic opportunities."

For half a century, Clevelanders knew Dr. Sawyer as a loyal and kindly private practitioner. He believed in "teaching patients," as well as students, the principles of physiology and personal hygiene. In this respect, he was ahead of his time in the practice of personal preventive medicine.

St. Vincent Charity Hospital was for 37 years the center of Dr. Sawyer's activities and teaching. Many local honors were awarded him during his long career, such as President of the Cleveland Medical Library Association and the degree of Doctor of Humanities from the University in 1941.

For several years, Dr. Sawyer had been in failing health following a cerebral vascular accident, but never lost his kindly interest in people and in medicine. He spent his winters in Vero Beach, Florida. His death came quietly at his old hospital home, "Charity," where he was Emeritus Chief of Staff since 1932.

V. C. ROWLAND, M.D., F.A.C.P.,  
Cleveland, Ohio

# ANNALS OF INTERNAL MEDICINE

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## TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN: REPORT OF CASES TREATED WITHOUT ANTI-COAGULANT AGENTS\*

By JESSAMINE R. GOERNER, M.D., ARTHUR J. GEIGER, M.D., and  
FRANCIS G. BLAKE, M.D., F.A.C.P., *New Haven, Connecticut*

THE attempt to cure subacute bacterial endocarditis with penicillin was a natural sequel to similar earlier efforts with the sulfonamide group of drugs, with which the results had proved successful in sporadic cases.<sup>1</sup> Limiting factors in the control of the infection with the sulfonamides have included the resistance of the usual causative organism, the *Streptococcus viridans*, and the toxicity of the sulfonamide compounds when administered in the large doses and long courses required to achieve prolonged bacteriostatic concentrations in the body. Although the resistance of the *Streptococcus viridans* to penicillin is generally known to be relatively high as compared with most other pyogenic cocci, inhibiting concentrations have been reasonably attainable both in vitro and in vivo. Moreover, the non-toxic nature of penicillin gave to this new drug an advantage not possessed by any other chemotherapeutic agent previously used in the treatment of this disease.

Our experience in the treatment of subacute bacterial endocarditis with penicillin is divisible into two epochs: (1) a period during the year 1942 when treatment consisted of relatively small doses and short courses with uniformly unsuccessful results and (2) the current period, beginning early in 1944, during which massive dose therapy has been applied with highly gratifying clinical effects. Because our earlier and our current experiences are so widely different, both in practice and in results, each period is presented separately in Sections I and II which follow.

\* Received for publication June 14, 1945.

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn., and the Medical Service of the New Haven Hospital.



# SECTION I CASES TREATED WITH RELATIVELY SMALL QUANTITIES OF PENICILLIN

Four cases of subacute bacterial endocarditis were treated with penicillin in 1942. The clinical features, therapy and results in this preliminary group are summarized in table 1. It will be noted that the doses and courses of

TABLE I  
Low Dose Penicillin Therapy in Subacute Bacterial Endocarditis, 1942

| Patient Unit No        | J. So B-33258   | L. S. 66584   | J. M. B-29573  | M. M. B-34154   |
|------------------------|---|---|--|---|
| Sex—Age                | F—10 yrs  | F—20 yrs  | M—25 yrs   | F—36 yrs  |
| Type Heart Disease     | Congenital (i-v septal defect)  | Rheumatic (mitral)  | Rheumatic (aortic & mitral)  | Rheumatic (mitral)  |
| Duration S B E         | 1 month   | 4 months  | 3 5 months   | 3-4 weeks   |
| Organism Colony Counts | Strep vir 175-240 col /c c  | Strep vir 80-200 col /c c   | Strep vir 2-7 col /c c   | Hem Staph alb (Coagulase +, Mannite +) 12-40 col /c c   |
| Penicillin Resistance  | 0.04 u/c c  | 0.005-0.01 u/c c  | 0.04 u/c c   | 0.04->0.1 u/c c   |
| Penicillin Therapy     | Days Therapy  | 14  | 28   | 18  |
|                        | Dates of Therapy  | 9-3-42 to 9-11-42   | 6-25-42 to 7-24-42   | 10-3-42 to 10-21-42   |
|                        | Doses and Routes  | 5000 u q 4 hr Intermittent Intramuscular  | 5000 u q 4 hr i-v for 10 days<br>10,000 u q 1 hr i-v for 17 days   | 10,000 u q 4 hr i-v for 13 days<br>10,000 u q 1 hr i-v for 3 days<br>5000 u q 1 hr i-v for 2 5 days   |
|                        | Total Course  | 210,000 u   | 110,000 u  | 1,380,000 u   |
| Result                 | During therapy fever diminished and col counts of blood cultures fell to 32-13/c c. Result failure. | During therapy fever diminished and cultures of blood were less heavily positive (0-62 col /c c). Result failure. | Fever and symptoms notably diminished during therapy but blood cultures intermittently positive. Result failure. | Blood culture became either sterile or yielded only light growth (0-3 col /c c) between 10-7-42 and discharge date of 10-27-42. Result failure. |
| Follow up              | Died 12 mo. later.  | Died 3 mo. later.   | Died 7 mo. later.  | Died 6 wks. later.  |

penicillin ranged from a daily dose of 30,000 units for eight days in one case, to one or 10,000 units for 18 days in another. The penicillin was injected intramuscularly or intravenously in fractionated doses at four-hour intervals. In one case intravenous injections were given hourly for five days. Although the results in all these cases were failure, the therapy was not

death within a year, it is interesting to note, in retrospect, that in all there was either temporary abolition or definite decline in fever, and the blood cultures either became sterile or yielded definitely scantier growth during these short courses with relatively small doses

Treatment employing much larger doses and longer courses was not feasible for this disease in 1942 because of the inadequacy of penicillin supplies for civilian use, and further efforts were postponed

## SECTION II CASES TREATED WITH MASSIVE QUANTITIES OF PENICILLIN

Early in 1944 we resumed therapeutic investigation of subacute bacterial endocarditis, following publication of the report by Loewe, Rosenblatt, Greene and Russell,<sup>2</sup> of the apparent cure of seven consecutive cases. This unique result had been achieved through the use of penicillin in massive doses supplemented by heparin, and administered over prolonged periods.

Our practice in the treatment of this disease has differed from that of Loewe and his associates chiefly in the omission of heparin. This simplification permitted evaluation of the effect of concomitant anticoagulant therapy.

*Dosage of Penicillin*\* The basic plan of therapy was to treat each patient with about 240,000 units of penicillin daily for three to four weeks. A larger dose or longer course might be dictated in any case by unusually high resistance of the infecting organism to penicillin in vitro, unsatisfactory serum penicillin levels or unfavorable clinical course. Each patient therefore received 5,000,000 or more units of penicillin.

*Technic of Administration* The penicillin was usually given by continuous intravenous infusion maintained day and night. Intramuscular injection of 20,000 units at two-hour intervals was employed through the entire course of treatment in only one case, but occasionally served during short periods of interruption of the continuous intravenous therapy. Continuous, slow intramuscular infusions were tried for several days in a few cases largely because of experimental interest in this technic.

For the continuous intravenous infusions the daily quantity of penicillin was dissolved in not more than 1,500 c.c. of physiological saline or 5 per cent glucose solution. In the beginning the infusion flask was enclosed in an ice jacket, later, when it was apparent that the potency of penicillin solutions did not deteriorate appreciably at room temperature, the cooling device was discarded with no unfavorable effects on the outcome of cases so treated.

The equipment included a gravity infusion set with a glass Murphy drip chamber, three-way stopcock and 21 gauge needle not longer than one inch. Any convenient vein in the forearm, wrist or hand (occasionally the foot or

\* The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigation as recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

ankle) was selected as the infusion site. When hand or wrist veins were chosen, the arm was bound firmly with adhesive tape to a small padded board in such a manner as to splint only the wrist, always leaving the elbow free. When the needle was placed in a forearm (or leg) vein high enough to avoid



Fig. 1

interference from movement of wrist or ankle, no splint was necessary (figure 1). The needle was inserted all the way to its shank, with as much of its length lying within the vein as possible. The shank and stopcock were securely fastened with adhesive tape to the skin and also to the splint if one was used.

This arrangement usually proved entirely painless and reasonably comfortable, offered relatively free use of the extremity, and permitted most

imum freedom of movement of the patient in bed or chair (figure 2) Such provisions for comfort are obviously important if the patient is to endure continuous venoclysis for several weeks With skilled venapuncture technic, the placement and retention of the needle were usually readily accomplished, cutting down on the vein was entirely unnecessary, and phlebothrombosis was rarely encountered The three-way stopcock was convenient for taking blood,\* and for clearing an obstructed needle The infusion was usually left undisturbed for several days, often as many as five, when a completely fresh assembly was introduced and a new vein on another extremity was



FIG 2

cannulated Infusion chills were rarely encountered Regulation of the rate of infusion was accomplished by means of a simple screw-clamp † on the infusion tubing and facilitated by the transparent drip chamber, through which the drops could be watched by either the patient or an attendant Special nursing was quite unnecessary, but we believe that the responsibility for attending to the details of the therapeutic regimen should rest upon a single interested individual or team

*Laboratory Controls* Several unequivocally positive blood cultures were a prerequisite for treatment in each case herein reported Observations included determination of the sensitivity of the infecting organism to penicillin, and of the penicillin serum levels during therapy The clinical course was

\* Blood drawn for serum penicillin estimations was not, however, obtained through this stopcock but always by direct venipuncture of the opposite arm to avoid the erroneously high penicillin concentrations present in the infused vein

† Recently we have found the special Tunnel Clamp of the Harvard Apparatus Co., Dover, Mass., advantageous in maintaining an even rate of flow

followed by the usual charting of vital signs and weight, by frequent blood cultures, by periodic blood counts, urine examinations and determinations of the sedimentation rate. Other special studies included electrocardiographic and roentgenographic examinations.

*Selection of Cases* Provided that the clinical syndrome of bacterial endocarditis was present and that the diagnosis was confirmed by several positive blood cultures yielding identical organisms in number greater than just an occasional colony or two per plate, the selection of cases was relatively unrestricted. During the 16 months covered by these experiments only four cases were not treated, two died shortly after admission, a third was rejected because the infecting organism was a gram negative bacillus. The fourth was an old man who refused treatment.

*Presentation of Cases* Since early 1944, 12 cases of subacute bacterial endocarditis have received massive penicillin therapy; a brief summary of each case follows.

#### CASE REPORTS

*Case 1* (figure 3) F S, a 35 year old barber, had no past history of rheumatic infections. He had been ill six months with weakness, fever, night sweats, a 20 pound weight loss, and evanescent pains. A bacteriological diagnosis of subacute bacterial endocarditis had been established in January 1944. The patient was in good physical condition when admitted for treatment in March 1944. He had a loud mitral systolic apical murmur, a palpable spleen, occasional petechiae, fever, increased erythrocyte sedimentation rate, moderate anemia, microscopic hematuria, and blood cultures that proved repeatedly positive for a *Streptococcus viridans* (3 to 30 colonies per c.c.) which was inhibitable by penicillin in a concentration of 0.01 unit per c.c. Treatment was with penicillin in doses of 20,000 units injected intramuscularly every two hours day and night for three weeks, the total amount given was 5,000,000 units. Petechiae, fever and hematuria soon disappeared, blood cultures promptly became sterile, and the sedimentation rate fell from 40 to 4 mm per hour (Westergren method). Since termination of therapy on March 30, 1944 the patient has gained 30 pounds in weight. 30 consecutive blood cultures have been sterile, the sedimentation rate has remained normal, and there has been no clinical evidence of recurrence of bacterial endocarditis. The heart murmur has grown softer. In August 1944, 14 teeth with perirapical abscesses were extracted in the course of a week without incident while penicillin was given prophylactically. The patient continues well and has been back at his work for 10 months.

This was the first case treated successfully with penicillin in our group. It was the only one in which the therapy consisted entirely of intramuscular injections.

excellent physical condition when she was transferred to us, but as evidence of continuing infection there were fever, moderate anemia, microscopic hematuria, a palpable spleen, and blood cultures repeatedly positive for *Streptococcus viridans* (86 to 108 colonies per c c), whose penicillin inhibition level was 0.03 unit per c c. Penicillin, given in doses of 240,000 units daily for 25 days by continuous infusion yielded

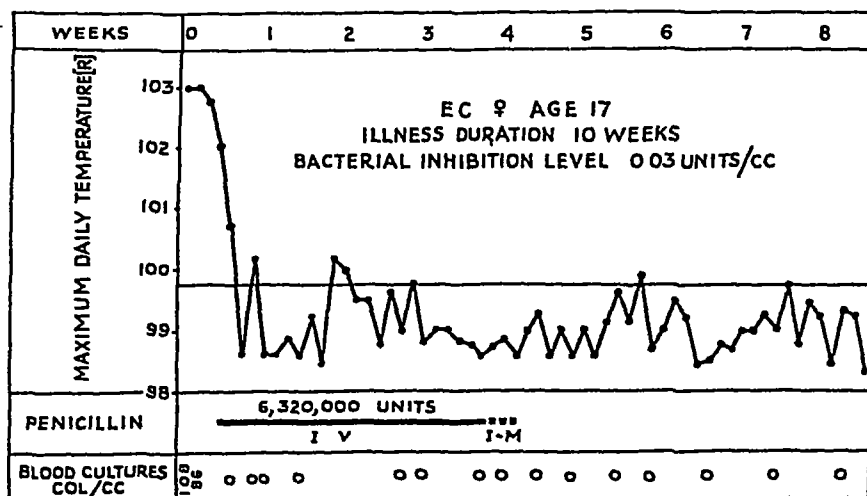
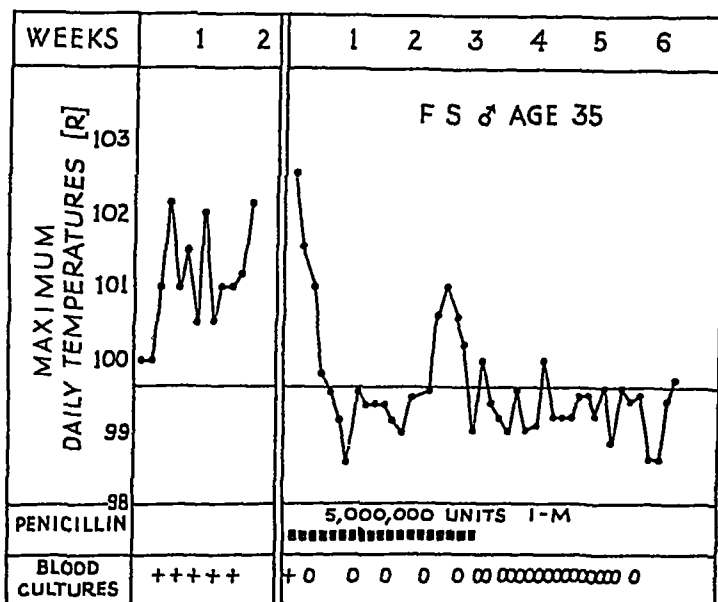
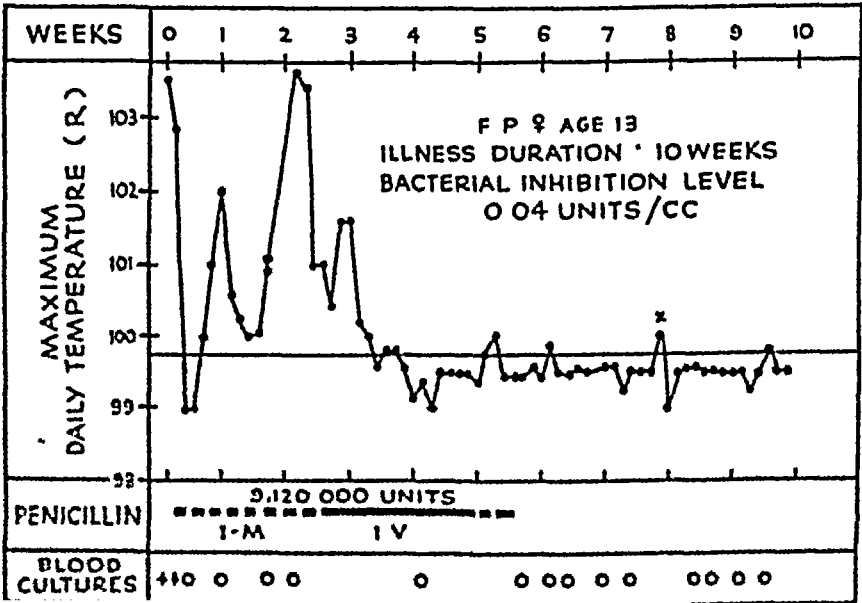
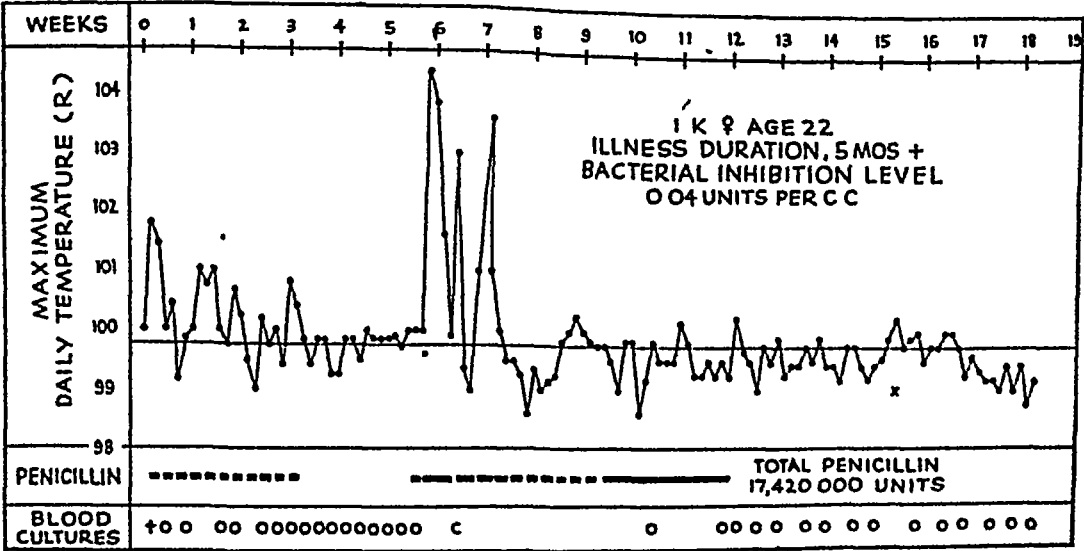


FIG 3 (above) Case 1

FIG 4' (below) Case 2

serum levels of 0.12 to 0.14 unit per c c. The temperature declined to normal within a few days after beginning treatment, the blood promptly became sterile, the splenomegaly and the anemia disappeared, and the patient became asymptomatic. During the last week of therapy a tooth with a periapical abscess was extracted. The apical systolic heart murmur grew gradually softer and less widely transmitted. Only after four months did the sedimentation rate remain within normal limits. The patient

gained 15 pounds in weight since her illness, and all of the 16 follow-up blood cultures continued sterile. She had been at school since September 1944 and was in excellent health at the time of this report



**Case 3 (figure 5)** I K, a 22 year old social service worker, had had rheumatic fever at the age of 10 which resulted in mitral stenosis and insufficiency, and aortic insufficiency. Symptoms of bacterial endocarditis dated back to October 1943, and blood cultures had yielded 91 to 120 colonies of *Streptococcus viridans* per c.c. Treatment at another hospital from January to April 1944 included courses of sulfadiazine, sulfamerazine, typhoid vaccine, and repeated blood transfusions, all had been unavailing. The patient came to us on April 21, 1944 in moderately poor physical condition seven months after the onset of symptoms. At that time a few skin petechiae were noted, and the blood cultures grew *Streptococcus viridans* (50 colonies per c.c.) whose penicillin inhibition level was 0.04 unit per c.c. Penicillin was given intramuscularly in two-hourly doses of 20,000 units with prompt sterilization of the blood and a suggestive decline in temperature. The serum penicillin levels declined from 0.3 unit per c.c. at 30 minutes following injection to a mere trace at 120 minutes. Treatment was suspended at the end of three weeks for experimental reasons, although persistence of borderline fever and minor embolic phenomena argued against cure. Treatment with penicillin was, therefore, resumed. On the following day acute splenic infarction occurred. In the second course the drug was given largely by the intravenous route, with occasional interruptions and substitutions of brief intramuscular courses due to difficulties with the intravenous drip. Because of a persistent febrile and subfebrile course and increased sedimentation rate, the daily dose of 240,000 units of penicillin was raised after 21 days to 360,000 units per day, and the increased dose was maintained conservatively for 25 days longer. Therapy at this level yielded serum penicillin concentrations of 0.15 to 0.20 unit per c.c. Treatment was finally stopped on July 12, 1944, when the patient had received a total of 17,420,000 units in two courses totalling 10 weeks. Since then she has been afebrile, she has gained 30 pounds in weight, 18 blood cultures have all been sterile, and regular menstruation has returned. The sedimentation rate has always remained elevated, but this could be attributed to a mild chronic mastoiditis due to *Staphylococcus aureus*. Shortly after discharge the patient had two episodes of nocturnal dyspnea, whereupon she was digitalized. She has since remained asymptomatic and is about to resume her occupation.

Although there was no bacteriological proof that the initial three weeks of therapy with 5,000,000 units failed to cure, this conclusion seemed warranted from the unfavorable clinical course at that time. Moreover, even after three more weeks of treatment we were impelled to continue penicillin in larger doses for about three weeks longer before the desired afebrile and asymptomatic condition seemed finally established. The development of early left ventricular failure (nocturnal dyspnea) during convalescence suggested that the aortic valve had suffered increased damage as a result of the infection, digitalization and unusually long restriction of physical activity seem to have controlled this complication.

**Case 4 (figure 6)** F P, a 13 year old schoolgirl, had had rheumatic fever at the ages of 8 and 10 and had developed mitral stenosis and insufficiency. The symptoms of subacute bacterial endocarditis, which included minor embolic phenomena had begun about five months before hospitalization on May 16, 1944. The patient had lost 15 pounds in weight, and her physical condition on admission was only fair. She had a hypochromic anemia (hemoglobin 10 gm.), leukocytosis (17,000 cells/cu. mm.) and persistent microscopic hematuria. Blood cultures yielded *Streptococcus viridans* (25 to 80 colonies per c.c.) whose penicillin inhibition level was 0.04 unit per c.c. Treatment was begun with 240,000 units of penicillin daily in two hourly intramuscular doses of 20,000 units. The serum penicillin levels attained ranged from 0.3 unit per



c c at one-half hour following injection to less than 0.05 unit at two hours. At the end of two weeks, during which the blood cultures remained sterile, the clinical response was considered poor because of occasional recurrence of petechiae, and persistence of fever, malaise, hematuria, anemia and increased sedimentation rate. At this time the mode of administration was changed to constant intravenous infusion employing the same total daily quantity of 240,000 units of penicillin which yielded serum penicillin levels of from 0.14 to 0.10 unit per c c. Within five days fever disappeared, symptomatic improvement was definite, menstruation returned after six months of amenorrhea, hematuria ceased, and the sedimentation rate declined toward normal. After 22 days of intravenous therapy the penicillin was discontinued on June 22, 1944. The patient had received a total of 9,120,000 units. She was gradually mobilized at the end of two uneventful weeks and discharged a month following termination of treatment. She gained 23 pounds during the following several months, 22 consecutive blood cultures were sterile, and the patient returned to high school in the fall of 1944. She remained in excellent health until January 1945 when acute follicular tonsillitis developed and was followed by several weeks of fatigue and mild joint pains, but fever did not recur, weight remained constant, and blood cultures and blood counts remained normal. Tonsillectomy was performed in May, 1945, under protection of penicillin therapy given for five days.

This case offers evidence of the probable superiority of continuous intravenous infusion over two-hourly intramuscular injections of penicillin, for the prompt clinical remission we usually see with effective therapy did not occur until the change to continuous intravenous infusion was made in the third week of treatment. The recent recurrence of acute tonsillitis followed by symptoms suggesting subacute rheumatic fever was regarded as an indication for tonsillectomy.

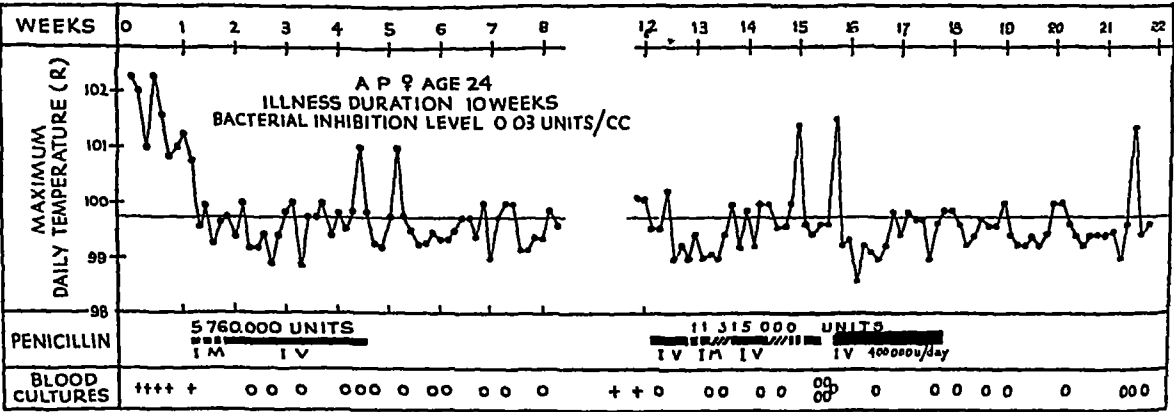


FIG 7 Case 5

Case 5 (figure 7) A P, a 24 year old seamstress, had had rheumatic fever at the ages of 14 and 16 which led to mitral stenosis and insufficiency. Symptoms of bacterial endocarditis dated back only six to 10 weeks before hospitalization on August 2, 1944 and included fever, sweats, weakness and weight loss, along with petechiae and Osler's nodes. Blood cultures repeatedly yielded a *Streptococcus viridans* (25 to 87 colonies per c c) which was inhibitable by 0.03 unit of penicillin per c c. Penicillin was given largely by the intravenous route for 23 days in daily doses of 240,000 units (total 5,760,000 units). The clinical response was considered satisfactory, but a few days after termination of treatment, the patient developed pain in the right

ankle, accompanied by loss of the dorsalis pedis pulse on that side, and slight fever. This was thought to be due to a non-infective embolus, for fever again disappeared and the blood remained sterile for about six weeks, although fatigue and diaphoresis continued. In the sixth and seventh post-therapy weeks fever and minor embolic phenomena reappeared, and four successive blood cultures were positive for *Streptococcus viridans* whose sensitivity to penicillin proved unchanged. Treatment was resumed, the penicillin being given at the rate of 240,000 units per day, by three different routes of administration (in order to compare the serum levels attained). Although the levels during continuous intravenous therapy ranged from 0.1 to 0.15 unit per c.c., the persistence of some malaise, occasional slight fever and minor embolic phenomena through 25 days of therapy led us to raise the daily dose to 400,000 units and to continue the course entirely by the intravenous route for 15 days longer. During this period the serum levels reached 0.3 to 0.4 unit per c.c., the clinical course seemed more satisfactory, and the sedimentation rate fell to normal and remained so through a month of further observation in the hospital during which sterility of the blood persisted. A single febrile rise two days before discharge was unexplained. After treatment was discontinued on December 8, 1944 the patient remained asymptomatic, menstruation was regular, she gained nine pounds in weight, sedimentation rate continued normal and 13 blood cultures were all sterile.

This was the only case in our group in which a patient who had been discharged as presumably well has had to return for retreatment so far. Inasmuch as the streptococcus originally obtained in her case was not preserved for comparison with the organism cultured some months later, we cannot definitely answer the question of relapse versus reinfection. We believe, however, that relapse had occurred, for the organism in both instances showed identical sensitivity to penicillin, and the clinical course following the second treatment period was characterized by subjective well being that was lacking after the initial course. The first course of 5,760,000 units should theoretically have been adequate for a patient whose physical condition was relatively good, whose infecting organism was of about average sensitivity to penicillin, and in whom the serum penicillin levels reached values several times greater than the *in vitro* inhibiting level for the organism. That therapy at this dosage was inadequate was implied not only by the relapse but also by the fact that repetition of this course still left doubt that cure had been effected, and it was not until the daily dose was raised approximately 50 per cent for two weeks longer that the total clinical picture assumed the aspects of cure. In the second and successful treatment period the patient received 11,315,000 units of penicillin, the total amount of drug expended was 16,995,000 units. Another simple lesson taught by this case is the irrelevance, so far as cure is concerned, of sterile blood cultures during and shortly after the period of active therapy with massive doses of penicillin.

*Case 6 (figure 8)* R. H., a 46 year old housewife had rheumatic fever in 1939 but was known to have had considerable hypertension and a murmur since at least 1931. In June 1944 hysterectomy and incidental appendectomy were performed. Following this the patient failed to regain her health, chronic fever was noted and treated ineffectually with sulfadiazine, migrating joint pains appeared and presently Osler's nodes also. A blood culture in September yielded *Streptococcus viridans*.

When admitted for treatment at the end of October, the patient had lost 10 pounds in weight, there were petechiae and moderate anemia, and the physical signs of aortic insufficiency were present along with evident left ventricular enlargement and blood pressure of 200 mm Hg systolic and 110 mm diastolic. Three successive blood cultures grew *Streptococcus viridans*, 30 colonies per c c, which proved inhibitable by penicillin concentrations of 0.03 unit per c c. Except for slight albuminuria and microscopic hematuria, the urinalyses were negative, specific gravity varied normally, and tests of kidney function and intravenous pyelography gave normal results.

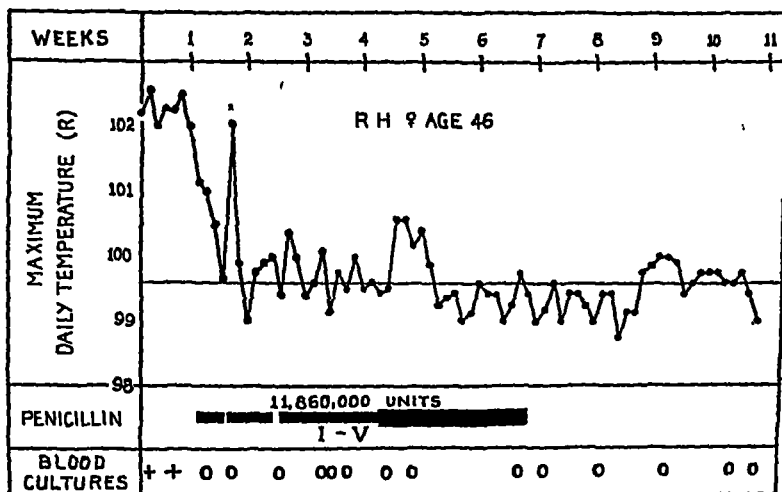


FIG 8 Case 6

Penicillin was given intravenously for 22 days in daily doses of 240,000 units which yielded serum penicillin concentrations of 0.08 to 0.13 unit per c c. Because of persistence of slight fever, microscopic hematuria and increased sedimentation rate, and also because there had been no gain in weight or improvement in the anemia, therapy was continued for 18 days longer with daily doses of 400,000 units of penicillin. During the fourth week of treatment a painful swelling developed over the right mandible, fever recurred, and a presumably abscessed upper right molar tooth was extracted with prompt subsidence of fever and local signs. The course thereafter was uneventful except that the aortic diastolic murmur changed from its originally blowing character to a louder and clearly musical murmur, this musical quality continued to be present intermittently. Since termination of treatment on December 8, the patient remained afebrile and well except for apprehension about her heart. She gained 13 pounds in weight. Each of nine blood cultures was sterile, the blood count became normal, but the sedimentation rate remained slightly elevated. She gradually increased her physical activity to include the lighter household tasks.

Our chief concern in this case was the pronounced hypertension, the aortic valvular insufficiency and the indications of heart strain seen in the cardiac enlargement and the electrocardiographic pattern of left ventricular hypertrophy and strain. Moreover, there was evidence in the markedly changing character of the aortic diastolic murmur that the vegetations were situated on this valve, and one would infer that increased injury of this valve would result from the bacterial endocarditis and its healing. Because all of these factors were regarded as a threat to the existing limited cardiac reserve, we maintained full digitalization of this patient since early in her treatment.

period, and we deliberately slowed her resumption of physical activity. One other detail of interest in her case was the electrocardiographic discovery of first degree A-V block (P-R 0.30 sec). This was present before digitalization and gradually diminished to 0.22 sec. Although she had no other

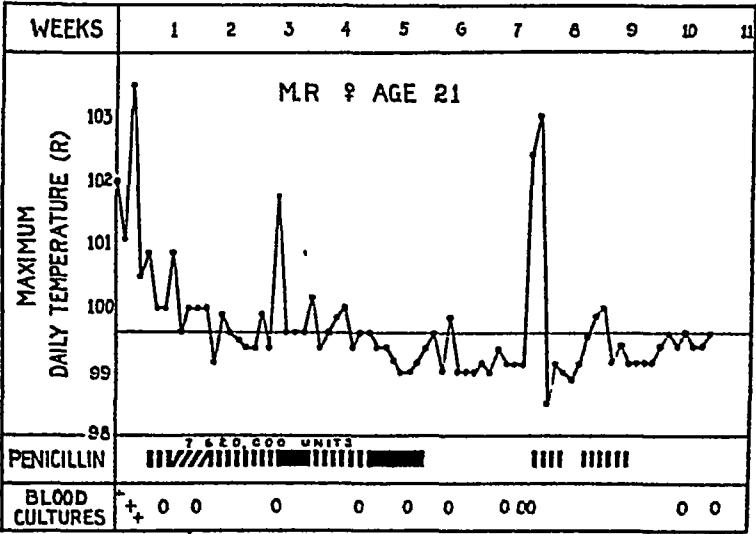
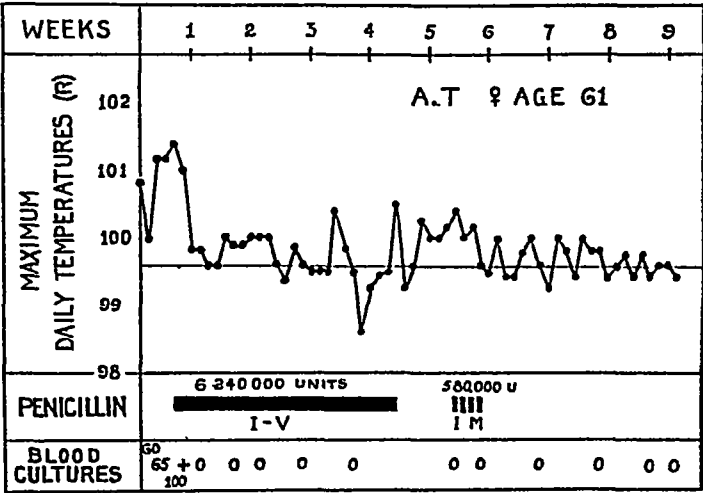


FIG 9 (above) Case 7  
FIG 10 (below) Case 8

clear evidence of acute rheumatic fever, we regard this changing conduction defect as evidence of subsidence of active rheumatic carditis which has been described as a common accompaniment of subacute bacterial endocarditis.

Case 7 (figure 9). A.T. the 62 year old wife of a physician, had enjoyed excellent health all her life. No heart murmurs had been detected at three routine physical examinations by two different internists over the past six years. Ill health began insidiously during October 1944 with fatigue, anorexia, weight loss and

light sweats, fever became apparent in December. Study at another hospital early in January disclosed repeatedly positive blood cultures. When transferred to us for treatment on January 11, 1945 this patient exhibited moderate fever, slight pallor, a loud, long and harsh apical systolic murmur with wide transmission, hemoglobin of 1 gm, a minimal albuminuria, and increased erythrocyte sedimentation rate. Three successive blood cultures yielded *Streptococcus viridans* (60 to 100 colonies per c.c.) whose penicillin inhibition level was 0.02 unit per c.c. Penicillin was given by constant intravenous infusion for 26 days in daily quantities of 240,000 units, with resulting serum penicillin concentrations of 0.4 unit per c.c. Fever gradually diminished after the third day, symptomatic improvement was steady, and the course was uneventful except for three minor events: a transient and superficial thrombophlebitis eight days before treatment was stopped, a tooth suspected of periapical infection was extracted early on the last day of therapy, and one week later a painful subcutaneous swelling appeared over the mandibular region on the other side accompanied by slight fever. Penicillin was given by intramuscular injection for three days, and the swelling gradually subsided in 10 days. The patient was discharged on March 15, 33 days after termination of therapy. She had received a total of 6,820,000 units of penicillin. Eight successive blood cultures since February 10 were sterile. The patient continued well, gained 10 pounds in weight, and was gradually resuming normal activity.

This patient was the oldest in our group. The etiology of the cardiac lesion that underlay the bacterial endocarditis remains obscure; although she recalled sore throats in early life, there was no past history of rheumatic fever, heart murmurs had not been heard by competent examiners prior to the present illness, and the mitral valvular endocarditis was unaccompanied by circumstantial evidence (roentgenographic or electrocardiographic) of preexisting heart disease. Although the streptococcus concerned was quite sensitive to penicillin in vitro and the serum penicillin levels achieved were relatively high, the temperature response to therapy was not as prompt and sustained as one might have expected, and declined gradually to normal only in the post treatment weeks. However, this was counterbalanced by the surprisingly early and rapid disappearance of symptoms.

*Case 8* (figure 10) M. R., a 21 year old colored housewife, had no past history of frank illness until immediately following the birth of her third child on September 7, 1944, when her right knee became painful and swollen. This condition persisted for several weeks, was followed by abdominal pain, profuse sweats and fever, and in mid-November by the appearance of pleural pain on the left side. The patient lost 20 pounds in weight through her pregnancy. When she was admitted on November 28, following a syncopal attack, she looked acutely ill, the throat was injected, the pupils were unequal, and nystagmus was observed bilaterally. The heart rate was 140 with gallop rhythm, the physical signs of mitral stenosis and insufficiency were present, and the blood pressure was 170 mm Hg systolic and 130 mm diastolic (hypertension gradually disappeared during the first two weeks of hospitalization). Attempts to prove a gonorrheal pelvic infection by local examinations and by cultures of the urethra and uterine cervix were unsuccessful. Three successive blood cultures were positive for *Streptococcus viridans* (3 to 6 colonies per c.c.), the penicillin inhibition level of which was 0.02 unit per c.c. Treatment with penicillin in daily quantities of 240,000 units was carried on for the first 11 days either by two-hourly intramuscular injections or by continuous intramuscular infusion. The serum penicillin levels

attained with fractional therapy ranged from 0.4 unit per c.c. in the first half hour following injection to 0.05 unit per c.c. in the fourth half hour, with continuous intramuscular infusion the concentrations of penicillin in the serum fluctuated widely as illustrated by random blood samples which yielded 0.07 to 0.26 unit per c.c. Both methods of penicillin administration, especially the intramuscular drip, proved painful and objectionable to the patient and unsatisfactory to us in the serum penicillin levels obtained. Continuous intravenous infusion of the drug was, therefore, resorted to and maintained for 22 days longer with only brief interruptions for technical reasons when intramuscular injections were substituted. With continuous intravenous administration the serum penicillin levels ranged from 0.2 to 0.26 unit per c.c. In view of progressive clinical improvement and the maintenance of a practically afebrile state during the last two weeks of therapy, penicillin was discontinued after 33 days of treatment during which a total of 7,620,000 units had been given. In the third week of convalescence an acute and severe tonsillitis developed, and penicillin injections were resumed for two and one-half days with prompt cure of the infection. A week later tonsillectomy was performed and penicillin was again resumed prophylactically for five days. Further convalescence was uneventful, and the patient was discharged on February 10, 1945. She remained asymptomatic, her weight increased 42 pounds, recent erythrocyte sedimentation rates were normal, and 15 consecutive blood cultures taken since termination of treatment on January 4, 1945 were sterile. Since discharge the original hypertension, which had disappeared during hospitalization returned, and a hypochromic anemia (hemoglobin 9 gm.) persisted in spite of prolonged treatment with iron. The cause of the anemia is obscure, urines have been persistently normal with specific gravity showing usual range of variation and blood non-protein nitrogen has never been elevated.

This case was one of several in which we attempted to administer penicillin by constant intramuscular injection using a very slow rate of drip, but the method proved unacceptable because it was too painful, the rate of drip was relatively uncontrollable, and the resulting serum penicillin levels proved undesirably variable. Tonsillectomy was performed because the patient had had two attacks of tonsillitis during her hospitalization. We believe that tonsillar infection is a source of bacteremia and threatens reinfection of the endocardium in these vulnerable patients.

*Case 9* J. S., an 11 year old schoolgirl suffered acute rheumatic fever at the age of 7. Although a "leaking valve" developed, she observed no restraints and was largely asymptomatic until mid-November 1944, when fatigue, anorexia, sweats and ankle pains developed. Weight loss, pallor and petechiae were noted presently. Subacute bacterial endocarditis with *Streptococcus viridans* was diagnosed and confirmed by four positive blood cultures at another hospital late in December. She was given a blood transfusion, and a total of 1,000,000 units of penicillin was administered by hypodermoclysis in six days. Because fever remained high and the patient was not doing well, she was transferred to us on December 31. She looked wasted and was acutely and seriously ill, with temperature of 105° F. There were several petechiae on the extremities. The moderately enlarged heart presented gallop rhythm and a loud, harsh and widely transmitted apical systolic murmur accompanied by thrill. The spleen was palpable.

Penicillin was withheld pending the recovery of organisms from the blood for bacteriological studies. However, within the next day the temperature fell to normal and remained so for 18 days while daily blood cultures continued sterile. In view of the possibility that cure had been effected therapy was still withheld. Nevertheless

one of the original positive blood cultures was received. The organism was a streptococcus, that produced green hemolysis, fermented inulin, was not soluble in bile and proved inhibitable by penicillin concentrations of 0.02 unit per c.c. During the first six weeks of observation in the hospital the blood cultures were persistently sterile, fever reappeared only once for three days in association with a lateral pharyngeal space infection, probably of dental origin, the spleen receded in size, and a few pounds of weight were gained. That the child was not well, however, was suggested by her poor general appearance, persistence of high sedimentation rate, periodic recurrence of painful petechiae and two episodes of apparent embolization of the spleen, both accompanied by severe pain. When acute pharyngitis and tonsillitis, with fever, recurred for the third time in two months, it was decided to perform tonsillectomy as a prophylactic measure, and to offer at the same time a "protective" course of penicillin in an effort to resolve the therapeutic dilemma. Accordingly, penicillin was given by constant intravenous infusion in daily doses of 200,000 units for a week prior to and two weeks following the operation, which was performed on February 28, 1945. During six weeks' observation in the hospital following termination of therapy the patient improved in general appearance, her appetite increased, she gained 12 pounds in weight, and no further petechiae or embolic phenomena appeared. Since discharge on April 21, there was no further fever, and 13 follow-up blood cultures were sterile. It was noted that the systolic murmur lost its original harshness, the systolic thrill disappeared, and a soft, low-pitched apical diastolic murmur developed.

Although we were unable to establish bacteriological proof that the patient was uncured when she was transferred to our care, it seems unlikely that six days of treatment with a total of 1,000,000 units of penicillin would have sufficed. Moreover, the patient did not appear clinically well during the two months of subsequent observation, and this was in contrast to her general clinical improvement subsequent to the tonsillectomy and the administration of 3,900,000 units of penicillin during a 20 day period. We believe the second, rather than the first, course of therapy was the curative one. The development of the murmur of mitral stenosis, together with the change in character of the systolic murmur, we regard as evidence of fibrotic healing of the vegetations on the mitral valve.

*Case 10* (figure 11) R. B., an 18 year old schoolgirl, was known to have had a heart murmur since the age of 7, at which time she was confined to bed for one year. She had no cardiac symptoms and was always in good health until May 1944, when protracted illness began insidiously with headaches, malaise, weakness, fever and diaphoresis. "Pleurisy" (left side) and painful red spots on the fingers were additional incidents of this illness. She grew increasingly pale and lost 16 pounds in weight in five weeks. Following the demonstration of streptococci in the blood in July, treatment with penicillin was instituted at another hospital. Therapy consisted of three separate courses of intramuscular injections of 10,000 to 25,000 units at three and six hour intervals over a period of five and one-half weeks. She received a total of about 2,500,000 units of penicillin. Petechial phenomena persisted, and blood cultures continued to yield streptococci.

When admitted to the New Haven Hospital in September the patient looked moderately ill and was very thin and pale. There were fever and marked tachycardia. The large heart presented classical signs of mitral stenosis and insufficiency including a diastolic thrill. A cluster of petechiae was present on the chest, and the spleen was palpable. Laboratory studies revealed a moderate hypochromic anemia, a corrected

sedimentation rate of 40 mm per hour, sinus tachycardia with a rate of 150 per minute by electrocardiogram, and aneurysmal enlargement of the left auricle by roentgenogram. Each of five successive blood cultures yielded *Streptococcus viridans* (90 to 120 colonies per c c) whose penicillin inhibition level was 0.03 unit per c c. Penicillin therapy by constant intravenous infusion of 240,000 units per day was started on

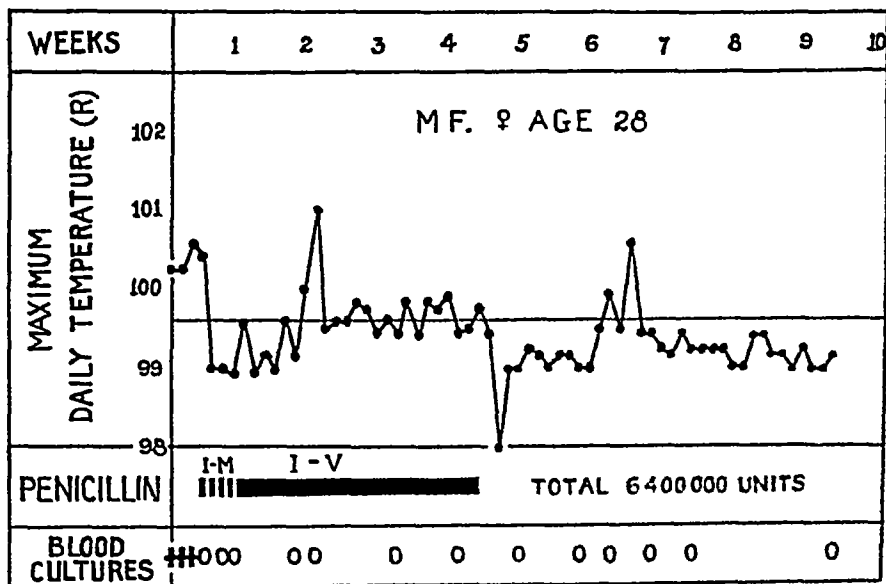
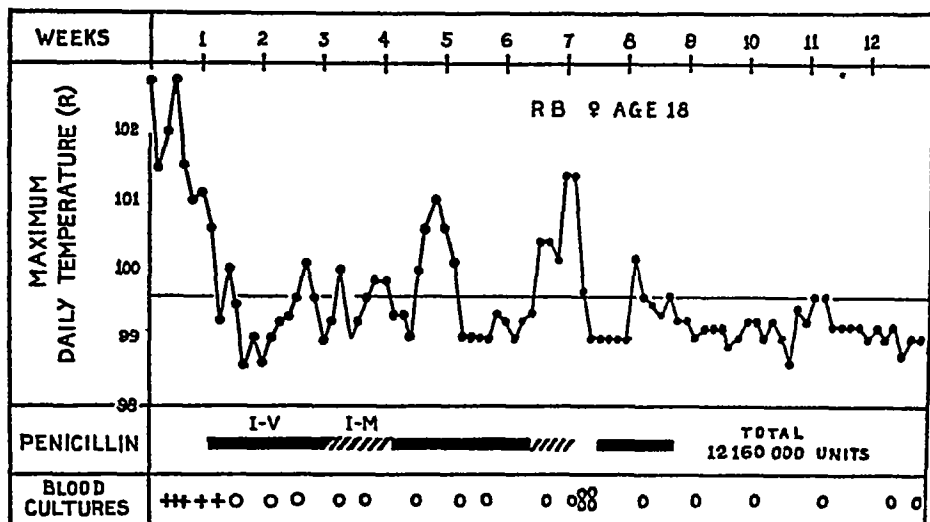


FIG 11 (above) Case 10  
FIG 12 (below) Case 11

September 16. Dosage at this level yielded serum penicillin concentrations ranging from 0.2 to 0.3 unit per c c. The temperature level fell promptly and the blood cultures remained persistently sterile after the first day of treatment. Symptomatic improvement was satisfactory and progressive menstruation returned; no further petechiae appeared and the patient gained several pounds in weight. However, an occasional slight febrile rise occurred, the high-grade tachycardia persisted and



ectopic ventricular beats appeared. Although it was believed that a subacute reactivation of rheumatic fever accounted for these disturbing signs, the undeniable possibility that bacterial endocarditis was still present led us to continue penicillin. In the fifth week right ventricular failure developed. The patient was digitalized, and 5 per cent glucose in smaller quantity was substituted for saline as infusion medium. The signs of congestive failure promptly disappeared and the course thereafter was uneventful except for two episodes of fever to  $101^{\circ}\text{F}$ , one episode was associated with a mild thrombophlebitis, the other followed a few days of administration of penicillin by continuous intramuscular infusion, which also produced severe muscle pain in the infused thigh without local or general signs of infection. Penicillin treatment was terminated at the end of 54 days, during which a total of 12,160,000 units had been given. Within the next two weeks the tachycardia subsided and the sedimentation rate fell to normal. All of 10 blood cultures taken since December 9, when penicillin treatment ceased, were sterile. The patient remained asymptomatic and afebrile, she looked very well, her blood count was normal, and she was gradually returning to a normal level of activity at home. Digitalis was being continued, although no evidence of congestive failure had reappeared.

We believe that failure of the original course of therapy which the patient had received before coming to us was attributable in part to discontinuous and insufficient treatment, and in part to the three and six hour spacing of the intramuscular injections with the result that the concentrations of penicillin in the blood were inadequate most of the time. Persistence in treatment for 54 days in this case was prompted by relatively minor evidence of continuing illness.

*Case 11* (figure 12) M F, a 28 year old colored housewife, had had acute rheumatic fever at age 13, and heart murmurs were detected two years later. The symptoms of subacute bacterial endocarditis began in October 1944, and included painful toe tips, arthralgia, amenorrhea, fever, weakness, anorexia and weight loss of 21 pounds. When admitted on January 3, 1945, the patient looked moderately ill. The classical signs of mitral stenosis were present. The spleen was not palpable but percussion dullness was increased. Three successive blood cultures were positive for *Streptococcus viridans* whose penicillin inhibition level was 0.03 unit per c.c. Penicillin was administered chiefly by constant intravenous infusion in daily quantities of 240,000 units, with which serum penicillin levels of 0.1 to 0.2 unit per c.c. were attained. During 26 days' treatment a total of 6,400,000 units was given. Except for the extraction of several abscessed teeth and for a mild febrile episode lasting two days, accompanied by pain and local swelling and tenderness of the right forearm (embolism), the course during treatment was uneventful, menstruation returned, the sedimentation rate declined to normal, and the patient gained seven pounds. During the early convalescent period there was a temporary recurrence of rheumatic fever, with mild arthralgia, slight temperature elevation, occasional ventricular ectopic beats, prolongation of A-V conduction time to 0.20-0.21 sec., and positive fibrinolysin test. The symptoms disappeared within two weeks, the P-R interval returned to the original value of 0.18 sec., and the temperature remained normal thereafter. The patient continued well, gained several more pounds in weight, and all of the 12 blood cultures obtained since termination of treatment on February 2, 1945 were sterile.

All the factors that promise therapeutic success were present in this case: brief duration of illness, good physical condition, location of the vegetations on the mitral rather than the aortic valve, a relatively sensitive infecting

organism, the ready attainment of satisfactory serum penicillin concentrations, and prompt clinical response to therapy. The presence of subacute rheumatic fever for a short time during early convalescence has been observed in two other patients in this group, the threat proved only transient in all. The finding of *Streptococcus viridans* in the sockets of several abscessed teeth confirms our impression that such foci of infection are potentially dangerous to these patients and should be eradicated.

*Case 12 (figure 13)* The case of D. J., a 32 year old telephone operator, has thus far been our single frank therapeutic failure. Although the patient's symptoms of migratory arthralgia, fever, weakness, headaches, anorexia and weight loss dated back only three months, she was already in very poor physical condition when she was admitted for treatment in February 1944. At this time she weighed but 80 pounds, had high fever and considerable anemia with leukocytosis. She was prostrate with severe pain apparently due to splenic infarction, the spleen was palpable, there were petechiae and Osler's nodes, and the signs of pulmonary infarction or pneumonitis were present over the left upper chest. The moderately enlarged heart presented a long and loud apical systolic murmur with wide transmission. Three successive blood cultures yielded *Streptococcus viridans* (7 to 40 colonies per c.c.) whose penicillin inhibition level was 0.05 unit per c.c. Three blood transfusions were given and on February 17 a course of penicillin was begun, which consisted of 5,490,000 units administered over 21 days in two-hourly intramuscular injections of 20,000 units each. Through this course the blood cultures remained sterile, the temperature declined steadily to normal, leukocytosis disappeared, the patient gained seven pounds, and seemed symptomatically improved. Eight post-therapy days were afebrile but then fever gradually returned, petechiae and bacteremia recurred.

On March 23, two weeks after termination of the first course of treatment, penicillin was again resumed in daily doses of 240,000 units, and in this course we attempted to keep the coagulation time of the blood at about 30 minutes through periodic subcutaneous depositions of heparin in Pitkin's menstruum\*. Again the trend of the fever was downward, the blood cultures became sterile and during this course no petechiae appeared. However, when penicillin was discontinued at the end of three weeks, bacteremia was evident by blood culture within 24 hours, the temperatures swung quickly upward again, and petechiae reappeared.

After a lapse in therapy for nine days due to lack of penicillin, and after proving that the resistance of the organism had not changed in vitro, treatment with penicillin and heparin was resumed on April 23. In this third course which lasted five weeks the patient received a total of 8,300,000 units, most of which was given in two-hourly intramuscular injections, but for 11 successive days near the end of the course the administration was by constant intravenous drip. The chief event of interest in this cycle was the development of a large retinal hemorrhage and visual scotoma attributable probably to the heparin. Although the temperature course was again downward, it did not reach sustained normal levels. As in the second course of therapy, the intense local reactions produced by the subcutaneous heparin were optimistically viewed as probably causing some fever. Since the patient seemed to be improving symptomatically, appetite and weight having increased and menstruation having reappeared, therapy was stopped on May 28. Bacteremia, renewed fever and petechiae promptly reappeared.

Because we had accomplished apparent cure in four other patients during the months of repeated failure in this case, we felt challenged to persevere in the therapy.

\* This material was furnished us by Dr. Leo Loew of Brooklyn, N. Y.

peutic efforts, and some hope was found in the fact that the organism had still not increased its resistance in vitro to penicillin. The final cycle of treatment was begun on June 7. In this course continuous intravenous drip was used almost entirely because it afforded more sustained and satisfactory serum penicillin levels (0.10 to 0.14

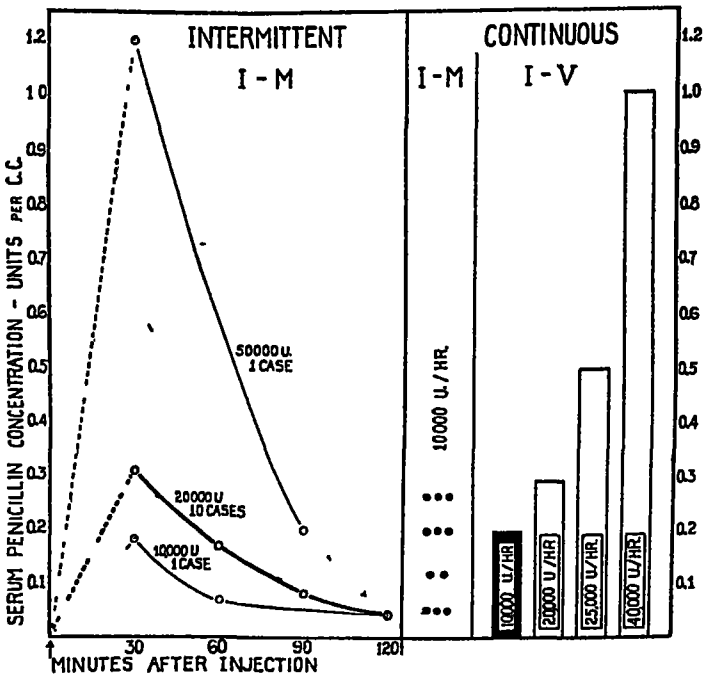
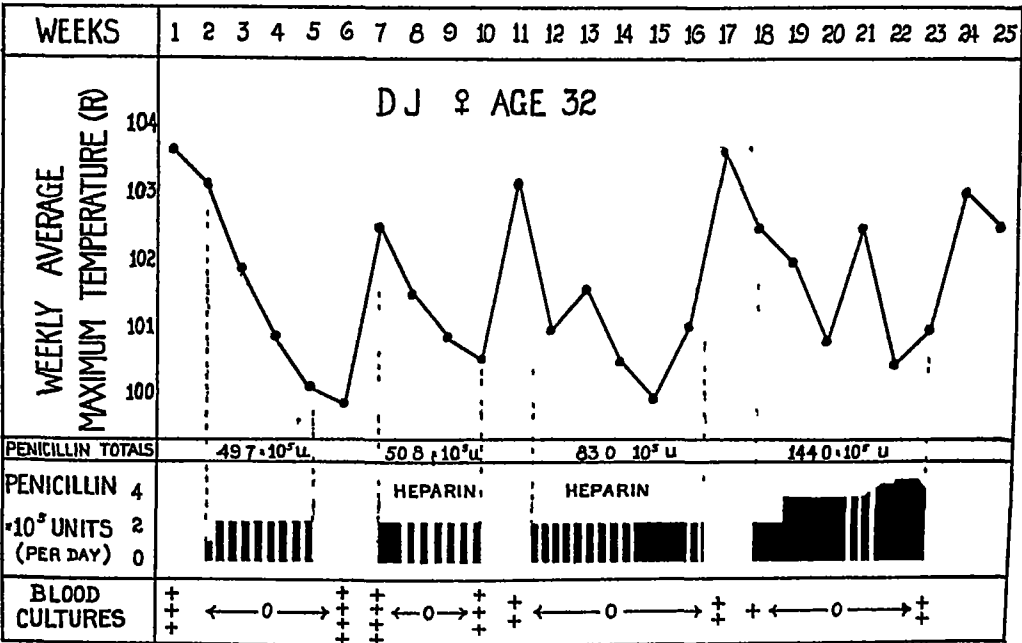


FIG 13 (above) Case 12  
FIG 14 (below)

unit per c c ) than two-hourly intramuscular injections of equivalent doses. Heparin was not added. When, after five days of treatment, new petechiae still appeared, the daily dose of penicillin was increased to 400,000 units. This yielded serum penicillin concentrations of 0.3 unit per c c. However, petechiae kept recurring and one

shower was preceded by a shaking chill and high fever. Although the blood cultures continued sterile, as usual during penicillin administration, we considered that active infection was implied, and the dose of penicillin was increased progressively to 500,000 units daily for the 11 final days. Promptly upon termination of the penicillin the temperature rose, bacteremia reappeared, and symptoms attributable to embolic phenomena returned. Family and physicians agreed that further therapeutic efforts be abandoned, and the patient was discharged. She died four months later at home, no necropsy was performed.

This patient received 32,750,000 units of penicillin during four months of active treatment. Why did failure occur in this single case? The duration of illness was no longer, the patient's physical condition was not much worse, and the infecting organism proved no more resistant to penicillin than those of other cases in this group which responded in much less time and to far smaller quantities of the drug. In retrospect, it is clear that the first and second cycles of therapy, in each of which promising signs of success occurred, were terminated prematurely when the temperature had barely reached normal. This was the first patient in the group to receive massive penicillin therapy. At that time the drug was not yet freely available, and the background of experience which should have indicated continuing penicillin instead of withdrawing it was lacking. Moreover, it had not yet been learned in the case of subacute bacterial endocarditis that with the two-hourly intramuscular injections of penicillin the serum concentration of the drug falls to undesirably low levels during the second hour, and that continuous intravenous infusion of equivalent amounts of penicillin represents more effective therapy. It seems possible that if the first course in this case had been continued for two or three weeks longer, and if the administration had been by the constant intravenous route, the result might have been as successful in this as in others. It is noteworthy that failure in this case was not due to increasing resistance of the infecting organism to penicillin, for during five months of more or less continuous administration of penicillin, the inhibition level *in vitro* remained unaltered.

The use of heparin in the second and third courses of treatment of this case, the only one in which anticoagulant medication was tried, did not change the outcome, and in view of the large retinal hemorrhage that appeared during heparin therapy, our feeling that anticoagulants were unimportant in the treatment, and potentially dangerous, was confirmed.

In the face of repeated failures to cure this patient, foci of infection from which bacteremia might be continuing were searched for in vain.

*Summary of Cases* Of the 12 patients who received massive penicillin therapy one was a therapeutic failure and 11 are alive and well. One patient relapsed shortly after discharge, she was retreated and has been well since mid-December, 1944. At the time of this writing in June, 1945, all 11 surviving cases are under our continued observation. The time that has elapsed since termination of the treatment courses has been from one to five months in three cases, from six to 10 months in four cases, and from 11 to 15

months in another four cases. The group included one middle-aged male and 11 females ranging in age from 11 to 63 years. The etiological type of heart disease in 11 was rheumatic, in one undetermined (case 7). Ten patients had mitral valvulitis alone, one had mitral and aortic valvulitis, and one had aortic valvulitis alone, the last had marked arterial hypertension as well. Minimal congestive failure in both of the aortic and in one of the mitral cases has been kept at an asymptomatic level with digitalis and slight limitation of activity. Minor embolic phenomena occurred during therapy in most of the cases and in the early convalescent period in about one third of the cases. These occurrences did not apparently alter the successful outcome.

*Streptococcus viridans* was originally recovered from the blood in each case. The infecting organisms were inhibited by penicillin concentrations ranging from 0.02 to 0.05 unit per c.c., and in no case was there evidence of acquisition by the bacterium of increased resistance to penicillin.

Treatment was chiefly by continuous intravenous infusion in all cases except one who received his penicillin entirely by the fractional intramuscular route. The daily doses of penicillin ranged from 200,000 to 600,000 units per day for total periods of from three weeks to nine and one-half weeks in the cases successfully treated. No untoward effects attributable to these large quantities of penicillin were noted.

#### SPECIAL LABORATORY STUDIES

*Serum Penicillin Concentration and Bacterial Inhibiting Levels.* Determinations of the sensitivity of the infecting organisms to penicillin and of the serum penicillin concentrations were carried out in all cases as a guide to therapy. The dose of penicillin was adjusted (from the basic minimum of 10,000 units per hour) so that the serum penicillin concentration was not less than three times the inhibiting level of the organism concerned in each case. Sensitivity assays were made at least twice on the organism obtained before therapy, and repeated on all subsequent positive cultures. Blood samples for serum concentration determinations during intravenous and continuous intramuscular treatment were drawn without preliminary adjustment of the drip rate. Hence, the levels obtained represent conditions prevailing during ordinary therapy rather than deliberately controlled experiment. Assays during intermittent intramuscular treatment were made on specimens taken every half hour for the two hours following an injection.

The sensitivity of the organisms was determined by a test tube method in which serial dilutions of penicillin in broth, each containing a drop of blood, were inoculated with the organism to be tested. A similar series of tubes, inoculated with a standard  $\beta$ -hemolytic streptococcus, accompanied each set of assays as a control.

Serum penicillin concentrations were determined in a similar manner, by inoculating dilutions of the serum with the standard hemolytic streptococcus.

Table 2 summarizes the serum concentrations observed in 11 of the treated cases of subacute bacterial endocarditis and four miscellaneous cases, using three modes of administration and a variety of doses. The figures recorded on each patient represent averages of several observations except for those on continuous intramuscular therapy, which are presented merely to show the wide fluctuations. Repeated assays in any one individual on continuous intravenous and intermittent intramuscular administration varied little provided the clinical conditions remained unchanged (i.e., in the ab-

TABLE II  
Average Serum Penicillin Concentrations (Units/c c) in Relation to  
Dose and Route of Administration

|      | Intramuscular        |                      |      |      |      | Continuous Intravenous |        |        |        |
|------|----------------------|----------------------|------|------|------|------------------------|--------|--------|--------|
|      | Single Dose<br>Units | Time after Injection |      |      |      | Units per hour         |        |        |        |
|      |                      | 30'                  | 60'  | 90'  | 120' | 10 000                 | 20 000 | 25 000 | 40 000 |
| I K  | 20,000               | 0.30                 | 0.15 | 0.07 | T    | 0.18                   |        |        |        |
| D J  | 20,000               | 0.25                 | 0.16 | 0.12 | 0.06 | 0.12                   | 0.30   |        |        |
| F P  | 20,000               | 0.30                 | 0.13 | 0.08 | 0.05 | 0.12                   |        |        |        |
| A P  | 20,000               | 0.40                 | 0.18 | 0.07 | 0.05 | 0.17                   | 0.35   |        |        |
| R B  | 20,000               | 0.30                 | 0.20 | 0.05 | 0.05 | 0.25                   |        |        |        |
|      |                      |                      |      |      |      | 0.40*                  |        |        |        |
| M R  | 20,000               | 0.40                 | 0.20 | 0.10 | 0.05 | 0.23                   |        |        |        |
| M F  | 20,000               | 0.26                 | 0.10 | T    | T    | 0.15                   |        |        |        |
| M S  | 20,000               | 0.20                 | 0.15 | 0.15 | 0.07 | 0.20                   | 0.60†  |        |        |
| W H  | 20,000               | 0.30                 | 0.18 | 0.09 | 0.06 | 0.10                   |        |        |        |
| D°   | 20,000               | 0.40                 | 0.20 | 0.07 | 0.05 | 0.23                   |        |        |        |
| E C  |                      |                      |      |      |      | 0.13                   |        |        |        |
| R H  |                      |                      |      |      |      | 0.10                   | 0.26   |        |        |
| A T  |                      |                      |      |      |      | 0.40                   |        |        |        |
| V H  | 50,000‡              | 1.2                  |      | 0.20 |      | 0.17                   | 0.23   | 0.50   |        |
| W L° | 10,000‡              | 0.18                 | 0.07 |      | 0.04 | 0.30                   |        |        | 1.0    |
| Avg  | 20,000               | 0.31                 | 0.17 | 0.08 | 0.04 | 0.20                   |        |        |        |

|     |      | § Continuous Intramuscular<br>10 000 Units per hour |      |      |      |      |      |  |
|-----|------|---|------|------|------|------|------|--|
| A P | 0.20 | 0.26  |      |      |      |      |      |  |
| M R | 0.07 | 0.26  |      |      |      |      |      |  |
| R B | 0.20 | 0.12  | 0.12 | 0.07 | 0.07 | 0.26 | 0.20 |  |

\* In congestive failure  
† In extremis  
‡ < 0.05 u/c c  
° Small children  
‡ Not included in Average  
§ Single determinations

sence of renal or cardiac failure). The levels obtained by the several methods of administration are compared graphically in figure 14. It is apparent that although the concentrations attained during the first hour after intramuscular injection are high, they fall off during the second hour to values probably quite ineffective in this disease. An equivalent dose per unit time given intravenously yielded a sustained therapeutic level higher than that at 60 minutes after injection. Extrapolation of the curve obtained from several observations on one patient after an injection of 50 000 units suggests that even with such massive doses no therapeutically effective amount of penicillin remains in the blood at the end of two hours.

*Erythrocyte Sedimentation Rate in Relation to Therapy* Sedimentation rates were estimated periodically by the Wintrobe method to determine whether such measurements were of aid in evaluating the progress and results of therapy. These data in the 11 successfully treated cases are summarized in table 3, in which the course of each patient may be followed by its case number.

TABLE III  
General Course of Corrected Sedimentation Rate

|     |   |                                 |
|-----|---|---------------------------------|
| I   | <i>Before Therapy</i>   |                                 |
| A   | Abnormally Rapid Rate   | All Cases                       |
| II  | <i>During Therapy</i>   |                                 |
| A   | Persistently Normal Rate                                      | No Cases                        |
| B   | Sustained Trend to Normal or to Near Normal Rates             | No Cases                        |
| C   | Irregular Course Varying between Normal and Abnormal          | Cases 5, 8, 11                  |
| D   | Sustained Abnormal Rates                                      | Cases 2, 3,* 4, 6, 7, 9, 10, 12 |
| III | <i>Early Convalescent Period (Up to 6 weeks post-therapy)</i> |                                 |
| A   | Persistently Normal Rate                                      | Cases 1, 5                      |
| B   | Sustained Trend to Normal or to Near Normal Rates             | Cases 10, 11                    |
| C   | Irregular Course Varying between Normal and Abnormal          | Cases 2, 3,* 4, 12              |
| D   | Sustained Abnormal Rates                                      | Cases 6, 7, 8, 9                |
| IV  | <i>Late Convalescent Period (After 6 weeks post-therapy)</i>  |                                 |
| A   | Persistently Normal Rate                                      | Cases 1, 4, 5, 9, 12            |
| B   | Sustained Trend to Normal or to Near Normal Rates             | Cases 2, 8                      |
| C   | Irregular Course Varying between Normal and Abnormal          | Cases 10, 11                    |
| D   | Sustained Abnormal Rates                                      | Cases 3* and 6                  |

\* Chronic mastoiditis

The sedimentation rate was always abnormally rapid before treatment, and normal values were eventually reached and maintained sooner or later in the convalescent period. It is evident, however, that the course of the sedimentation rate was entirely worthless as evidence of therapeutic success at the times when such an indicator would prove most helpful, namely, during the period of active treatment and in the early post-therapy weeks. The usual ultimate attainment of persistently normal values is simply minor corroborative evidence that the bacterial endocarditis has healed.

## DISCUSSION

In contrast to the uniform failure that attended our earlier efforts to treat subacute bacterial endocarditis with small quantities of penicillin is the signal success that is now being achieved with massive doses. A successful therapeutic result in 11 of 12 cases so treated indicates that this once highly fatal disease is now probably as susceptible of cure as any other serious pyogenic infection.

In the critical examination of alleged cures in cases of subacute bacterial endocarditis, two pertinent questions arise: (1) was the diagnosis correct, and (2) was the clinical recovery a permanent condition or merely a temporary remission, either spontaneous or therapeutic? The occurrence in acute rheumatic fever and other diseases of an occasional ephemeral light bacteremia with *Streptococcus viridans* has been clearly established.<sup>6</sup> It is

obvious that an erroneous diagnosis of subacute bacterial endocarditis may, therefore, be made. However, the cases here presented had persistent bacteremia, usually with high or moderately high colony counts, all but one had typical embolic phenomena, all but the few very early cases had the clinical features of a wasting disease with chronic fever, and none had prominent rheumatism to suggest that the true diagnosis was merely active rheumatic fever or myocarditis. The diagnoses were based on the criteria which, from past experience, have proved sound as judged from the typically fatal course in untreated cases.

All of the discharged cases except one (case 12, who was a frank therapeutic failure) have remained well, and several who were treated early in 1944 have enjoyed approximately a year of good health. Subacute bacterial endocarditis is characteristically a chronic disease, and though usually progressive to a fatal termination within a year, remissions lasting weeks and occasionally longer are known to occur. Moreover, Libman<sup>6</sup> has described a bacteria-free stage of the disease. In these rather rare cases, however, clinical sequelae and evidences of continuing disease are said to characterize the course. Thus, although cures in bacterial endocarditis cannot yet be established with assurance, permanent remission is considered a probability in the foregoing cases for the following reasons. In the first place, spontaneous clinical remissions of such completeness and duration are distinctly exceptional, if known at all, rather than common in this disease, and it would make a tenuous argument indeed to contend that these successive cases happened to represent just such remarkable clinical remissions. At least, such a statistical experience has never been reported in medical literature to our knowledge. Moreover, the clinical evidences of subsidence of active infection in each of the successfully treated cases occurring usually within the first week of penicillin therapy seem more than coincidental in a chronic disease. A more plausible question than spontaneous remission is whether the disappearance of clinical signs of infection in these patients represents a temporary therapeutic remission rather than a permanent cure. Only time can answer this question, for when the therapeutic remission is regularly found to exceed a year, cure seems certainly to have been achieved. This result is already being witnessed in the first several cases presented in Section II, and in many of the patients treated by Loewe and his group.<sup>7</sup> Even if such cases were still viewed as therapeutic remissions rather than cures, a great advance in the control of the disease would be implied, for if a month of therapy can provide a year or more of arrest in a relentlessly progressive disease, the achievement would be worth while.

The recurrence of bacterial endocarditis after several months in any of the successfully treated cases need not necessarily indicate reactivation of the preexisting disease, for it is not implied that successful treatment confers immunity, and reinfection is probably just as likely as ever to occur in these patients with acquired or congenital endocardial defects. Thus far we have encountered no apparent reinfection in any of our cases.



The proof of cure will also find its ultimate test when apparently cured patients die of other causes and become available for necropsy examination with careful histological and bacteriological study of the previously infected sites. That opportunity has not yet occurred in this group of patients, but a few such cases have been alluded to by others<sup>8,9</sup>.

Persistent failure in the cure of subacute bacterial endocarditis has been attributed to the relative drug-resistance of the infecting organisms, the toxicity of most antibacterial drugs when administered in large doses and long courses, and the theoretical inaccessibility of the viable organisms that become safely buried in progressive thrombotic accretions. Attack upon the latter barrier has been attempted with anticoagulant agents,<sup>2,9,10,11</sup> yet one may question the necessity of such supplemental treatment. It is conceivable that if the surfaces of vegetations can be kept sterilized for several weeks, epithelialization of the surface and fibrotic scarring of all or most of the thrombotic mass may effectively incarcerate and perhaps ultimately destroy bacteria lying beneath. That anticoagulant medication may be unnecessary was also suggested by Lichtman's statistical survey of the cures of bacterial endocarditis achieved with sulfonamide drugs.<sup>1</sup> The cure rate of 109 cases treated with heparin and sulfonamides was only 2.5 per cent higher than with sulfonamide compounds alone. It is noteworthy, therefore, that the use of anticoagulant agents as therapeutic supplements to penicillin has not proved necessary in the successful treatment of our cases. The maintenance of continuous heparin effect for weeks considerably complicates the technical management of these cases, the drug often causes fever which confuses the clinical course, and the administration calls for at least daily estimations of the coagulation times to guarantee proper control of the dosage. Heparin is potentially a dangerous drug, especially in a disease in which embolic phenomena are common and predispose to vascular injury with the threat of serious hemorrhage, particularly in the brain. The frequency of cerebral accidents in patients with bacterial endocarditis receiving anticoagulant medication had been repeatedly reported,<sup>11,12</sup> and it is recalled that our one patient (D J, case 12) who received heparin during two retreatment periods, developed a large retinal hemorrhage with persistent visual scotoma. Finally, heparin is expensive, the required daily amount actually costs more than the penicillin and adds hundreds of dollars to the cost of treatment of the average case. That heparin has proved unnecessary in our cases has been one of the gratifying results of our experiments. Whether heparin will prove advantageous in the treatment of far advanced cases with perhaps more massive vegetations, is yet to be learned.

In the light of current highly encouraging experience with penicillin in the control of subacute bacterial endocarditis, the consistent failures encountered earlier in our experience were obviously attributable to inadequacy of treatment in all respects: the daily doses were too small, the courses of treatment were too short, and in the use of fractional intramuscular dosage the three and four hour intervals between injections were apparently too long.

for effective antibacterial titers to be maintained. With the employment of massive doses in long courses and administration of the drug by routes designed to assure sufficiently high titers of penicillin in the blood, control of the infection is proving easily attainable in most cases. Some evidence for these opinions is given in table 4.

TABLE IV  
Treatment Results in Relation to Duration of Treatment and Total Quantities of Penicillin Administered

| Patient | Non-Curative Courses |                  | Curative Courses |                  |
|---------|----------------------|------------------|------------------|------------------|
|         | Days Therapy         | Total Penicillin | Days Therapy     | Total Penicillin |
| J So    | 85                   | 240,000 u        |                  |                  |
| L S     | 14                   | 440,000          |                  |                  |
| J M     | 28                   | 1,380,000        |                  |                  |
| M M     | 18                   | 1,800,000        |                  |                  |
| F S     |                      |                  | 21               | 5,000,000        |
| E C     | 16                   | 1,600,000        | 25               | 6,320,000        |
| I K     |                      |                  | 70               | 17,420,000       |
| F P     |                      |                  | 36               | 9,120,000        |
| A P     | 23                   | 5,760,000        | 40               | 11,315,000       |
| R H     |                      |                  | 40               | 11,860,000       |
| A T     |                      |                  | 26               | 6,820,000        |
| M R     |                      |                  | 33               | 7,620,000        |
| J S     | 6                    | 1,000,000        | 20               | 3,900,000        |
| R B     | 38                   | 2,500,000        | 54               | 12,160,000       |
| M F     |                      |                  | 26               | 6,400,000        |
| D J     | 120                  | 32,750,000       |                  |                  |

Of the various modes of administration of penicillin with which we have had experience thus far, the constant slow intravenous infusion seems to have been best both from the patient's standpoint of maximal comfort, and from the scientific standpoint of maintaining relatively constant and satisfactory serum levels of penicillin with utmost economy in the use of the limited supplies available until recently.

From the technical standpoint the continuous intravenous route is admittedly not the simplest, and its successful routine use requires skillful venoclysis technic and relatively close supervision of each case during the several weeks of therapy.

A therapeutic course consisting of about 250,000 units per day for four weeks is apparently proving adequate to treat the majority of the relatively early cases in whom physical deterioration is not notably advanced, and whose infecting organism is satisfactorily inhibitable. An especially favorable case, particularly one whose infecting organism is highly susceptible to penicillin, would undoubtedly respond to less intensive treatment whereas cases of more advanced disease and those with exceptionally resistant organisms probably demand large doses and a longer course.

Ideal control of the therapy and its proper experimental study call for bacteriological facilities permitting identification of the infecting bacterium,

estimation of its resistance to penicillin in vitro, and measurement of the serum penicillin titers obtained during treatment to assure that effective antibacterial therapy is actually being provided. It is still not known how closely the results of bacterial inhibition tests made in vitro can be translated into terms of effective serum penicillin levels required in vivo. Thus, if 0.04 unit of penicillin per c.c. of culture will inhibit growth of the bacteria in the test tube, will the administration of penicillin in amounts sufficient to yield a serum concentration slightly greater than 0.04 unit per c.c. be adequate to sterilize the blood stream and vegetations and bring about cure? In the absence of sufficient data to answer this question, and in the interest of conservative practice, an effort has been made to establish serum penicillin concentrations about three times greater than the in vitro inhibiting level of the bacterium concerned. In hospitals where ample facilities for management and study of these cases are available, the treatment of subacute bacterial endocarditis may now be considered a practical undertaking. Under circumstances where such facilities are not available and cannot be reached, treatment should not be denied but should be given empirically. The simplest therapeutic practice under such conditions would seem to be the injection of penicillin intramuscularly in doses of at least 30,000 units at intervals of not longer than two hours day and night for at least four weeks. Cure of many of the favorable cases would probably result, although the practice is admittedly wasteful of penicillin, and the occasional case harboring an unusually resistant organism would probably fail to be cured because of inadequate dosage.

### SUMMARY

Twelve patients with subacute bacterial endocarditis were treated with penicillin given in massive doses and prolonged courses. Eleven of these patients are alive and well, and in several cases more than a year has elapsed since termination of therapy.

Heparin proved unnecessary in the cure of the 11 successful cases, nor did its use alter the outcome of the single unsuccessful case.

Administration of penicillin in small doses and short courses failed to cure in all of four cases so treated in 1942.

Evidence is presented to show that of the three parenteral routes of administration employed, namely continuous intravenous infusion, continuous intramuscular infusion, and intermittent intramuscular injections at two-hour intervals, the first was the most satisfactory.

### CONCLUSION

Penicillin alone is an effective therapeutic agent for subacute bacterial endocarditis when the infecting organism is inhibitable by penicillin and provided that the conduct of treatment is carefully determined in each individual case.

*Addendum* regarding Case 10 (R B) On June 12, 1945, the patient was still asymptomatic, afebrile, and her blood cultures were sterile. On that day a tooth with periapical abscess formation was extracted following the prophylactic administration of a single injection of 400,000 units of penicillin-in-oil with beeswax. Two weeks later malaise reappeared with fever and positive blood cultures (*Streptococcus viridans*). Penicillin was again administered intravenously for three weeks in daily doses of 240,000 units, and the outcome was again apparent cure. On August 22 the patient was hospitalized with an acute illness including signs of meningeal infection, fever and headache. Repeated cultures of the spinal fluid and blood have remained sterile for bacteria but monilia have been grown from three cultures of the blood. All the other apparently cured cases reported above remain well at the time of this note, September 11, 1945.

## BIBLIOGRAPHY

- 1 LICHTMAN, S S Treatment of subacute bacterial endocarditis current results, *Ann Int Med*, 1943, xix, 787
- 2 LOEWE, L, ROSENBLATT, P, GREENE, H J, and RUSSELL, M Combined penicillin and heparin therapy of subacute bacterial endocarditis, *Jr Am Med Assoc*, 1944, cxliv, 144
- 3 KIRBY, W M M Stability of penicillin solutions at room and incubator temperatures, *Jr Am Med Assoc*, 1945, cxlv, 628
- 4 VON GLAHN, W C, and PAPPENHEIMER, A M Relationship between rheumatic and subacute bacterial endocarditis, *Arch Int. Med*, 1935, lv, 173
- 5 LICHTMAN, S S, and GROSS, LOUIS Streptococci in the blood in rheumatic fever, rheumatoid arthritis and other diseases, *Arch Int Med*, 1932, xlix, 1078
- 6 LIBMAN, E. A further report on recovery and recurrence in subacute bacterial endocarditis, *Trans Assoc Am Phys*, 1933, lviii, 44
- 7 LOEWE, LEO The combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, *Bull New York Acad Med*, 1945, xxi, 59
- 8 LOEWE, LEO Personal communication
- 9 DAWSON, M H, and HUNTER, T H The treatment of subacute bacterial endocarditis with penicillin (Results in twenty cases), *Jr Am Med Assoc*, 1945, cxlvii, 129
- 10 KELSON, S R, and WHITE, P D A new method of treatment of subacute bacterial endocarditis using sulfapyridine and heparin in combination Preliminary Report, *Jr Am Med Assoc*, 1939, cxiii, 1700
- 11 McLEAN, J, MEYER, B B M, and GRIFFITH, J M Heparin in subacute bacterial endocarditis, *Jr Am Med Assoc*, 1941, cxvii, 1870
- 12 KATZ, L N, and ELEK, S R Combined heparin and chemotherapy in subacute bacterial endocarditis, *Jr Am Med Assoc*, 1944, cxliv, 149

# ENDEMIC (MURINE) TYPHUS FEVER: CLINICAL OBSERVATIONS OF 180 CASES \*

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IN the period from January 1, 1929, to December 31, 1944, 180 cases of endemic (murine) typhus fever were observed in the Charity Hospital of Louisiana at New Orleans. Although several of these cases have been previously reported,<sup>1, 2</sup> our observation of approximately one-half of the entire series during the past three years warrants an analysis of these cases from the clinical viewpoint.

Both European and Mexican epidemic typhus have been introduced into the United States from time to time. One of the best known instances of importation from Europe was the Philadelphia epidemic, in 1836, when Gerhard<sup>3</sup> successfully differentiated the disease from typhoid fever. Despite frequent occasions when epidemic typhus has been introduced into the United States this type of typhus (louse-borne) has apparently never gained a permanent foothold in this country.

Mild typhus was first observed in the United States, in 1898, by Brill<sup>4</sup> of New York. Recent studies by Zinsser and his associates<sup>5</sup> indicate that "Brill's disease" may be a late recrudescence of classic epidemic typhus in individuals who have migrated to endemic areas. Endemic typhus was first reported in the South at Atlanta, Georgia in 1913.<sup>6</sup> Subsequent reports<sup>7, 8, 9</sup> in the next few years indicated that several towns along the southern Atlantic and Gulf Coast were endemic foci of the disease. In 1923, Maxcy and Havens<sup>10</sup> reported a number of cases in Alabama with a positive Weil-Felix reaction. Maxcy,<sup>11, 12</sup> in 1926, published reports of epidemiological studies which indicated the rat to be a reservoir of infection. It remained for Dyer and co-workers,<sup>13</sup> however, in 1931, to separate the louse-borne typhus of Europe from the sporadic typhus of the southeastern United States by demonstrating the rat flea to be the vector, and the rat the reservoir host of these endemic cases of typhus.

## ETIOLOGY

Although the Rickettsiae of murine typhus are closely related biologically to the etiologic agent of epidemic typhus, it is now recognized that two distinct varieties of the organism exist. *Rickettsia prowazekii prowazekii*, the etiologic agent of the classic epidemic human louse-borne disease, and *Rickettsia prowazekii mooseri*, the agent causing murine or endemic typhus.

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Morphologically, these two varieties of typhus Rickettsiae are identical, however, Mooser,<sup>14</sup> in 1928, pointed out that the virus of endemic typhus caused a pronounced scrotal reaction in guinea pigs as contrasted with the strain responsible for epidemic typhus

The two varieties of typhus Rickettsiae, like other Rickettsiae, are small organisms showing coccoid and bacillary forms. Apparent measurements of single organisms may vary in length from 1.2 to 1.6 micra and average 0.3 micron in width.<sup>15</sup> These Rickettsiae have been observed in chains ranging up to 40 micra in length. Rickettsiae do not pass readily through ordinary bacterial filters. They stain poorly or not at all with ordinary methods used in staining bacteria, but can be readily stained by the special methods of Castenada, Giemsa or Machiavello.<sup>16</sup> Rickettsiae fail to grow in ordinary media, but are easily cultivated in the various media employing living cells, the yolk sac of the developing chick embryo being one of the preferable methods.<sup>17</sup>

### TRANSMISSION

Endemic typhus has a reservoir in nature in the common rat, whereas epidemic typhus is transmitted from person to person by body lice (*Pediculus humanus*). The endemic variety is transmitted from rat to rat by rat fleas (*Xenopsylla cheopis*) and rat lice (*Polyplox spinulosus*). Although experiments to demonstrate the transmission of typhus by the bite of the rat flea alone have been uniformly unsuccessful, the feces of typhus-infected fleas have been found highly infectious. It would appear, therefore, that the infection is transmitted through this medium. This may take place by the rubbing of infected feces through skin abrasions, or perhaps in some instances by inhalation or ingestion.

### EPIDEMIOLOGIC FEATURES

As previously stated, the rat serves as the reservoir for murine typhus, however, an infected rat flea may recover from the infection and harbor the Rickettsiae for a month or more. Endemic typhus most often appears as a sporadic disease but may approach epidemic proportions, and under such circumstances transmission from man to man by the body louse is said to occur.<sup>14, 18</sup> The disease occurs most commonly among workers in food-handling establishments. In contradistinction to epidemic typhus, the endemic variety does not necessarily predominate among the poorer classes of people. The peak of prevalence is usually in the late summer and fall.

Endemic typhus is being recognized with increasing frequency in the United States, especially along the Atlantic and Gulf Coast, in the southern and the southwestern areas of the country.

### PATHOLOGY

Gross pathologic changes include little more than the partially faded exanthem, occasionally petechial hemorrhagic lesions which may persist

slight enlargement of the spleen, some degree of visceral cloudy swelling, and at times bronchitis and bronchopneumonia. Thrombosis of the larger vessels is rarely seen in the murine variety of typhus. The brain and meninges characteristically appear normal or present only evidences of congestion.

In 1914, Fraenkel<sup>19</sup> described the specific histologic lesions of typhus appearing in association with the blood vessels of the skin. Microscopically, the essential pathologic change is a generalized proliferative endangitis, usually involving the arterioles, precapillaries, capillaries, and venules, and infrequently affecting the larger vessels. These lesions are due to growth of *Rickettsiae* in the endothelial cells lining the vessels. In the smaller vessels, swelling and proliferation of the affected endothelial cells may cause occlusion. Thrombosis is a result of damage to the endothelial cells of larger blood vessels. An accumulation of mononuclear cells forming small nodular lesions in the perivascular regions of smaller blood vessels is considered a characteristic feature of the disease. These lesions occur in practically all organs, but are most prominent in the brain and skin. The predominant pathologic difference between the two types of typhus is the lesser degree of extensiveness and severity seen in the endemic form of the disease.

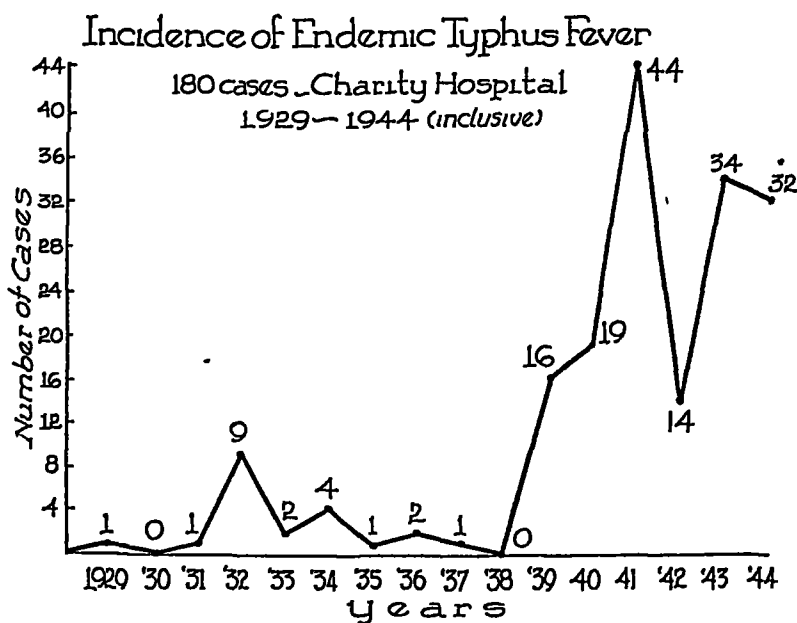


FIG 1 Annual incidence of 180 cases of endemic (murine) typhus fever at Charity Hospital of Louisiana at New Orleans for the years 1929-1944 inclusive

### CLINICAL FEATURES

Although approximately 200 cases of typhus have been diagnosed clinically at Charity Hospital, only 180 of these were found acceptable for the diagnosis of typhus fever according to the following criteria (1) significant or rising agglutination titers, and (2) clinical picture considered characteristic of endemic typhus. No case was included in this series unless agglutinins for OX<sub>19</sub> in a titer of 1:160 or greater were demonstrated.

*Incidence* As shown in figure 1, the highest incidence of typhus fever at Charity Hospital occurred in 1941, with the next greatest frequencies in 1943 and 1944. Also demonstrated in figure 1 is the increasing incidence of typhus fever since 1939. This increasing incidence corresponds to the increase in the United States as reported by the United States Public Health Service. Although the physician's attention is being focused more and more on typhus fever as a cause for obscure fevers, it is doubtful that this increase could be entirely explained on the basis of increased recognition.

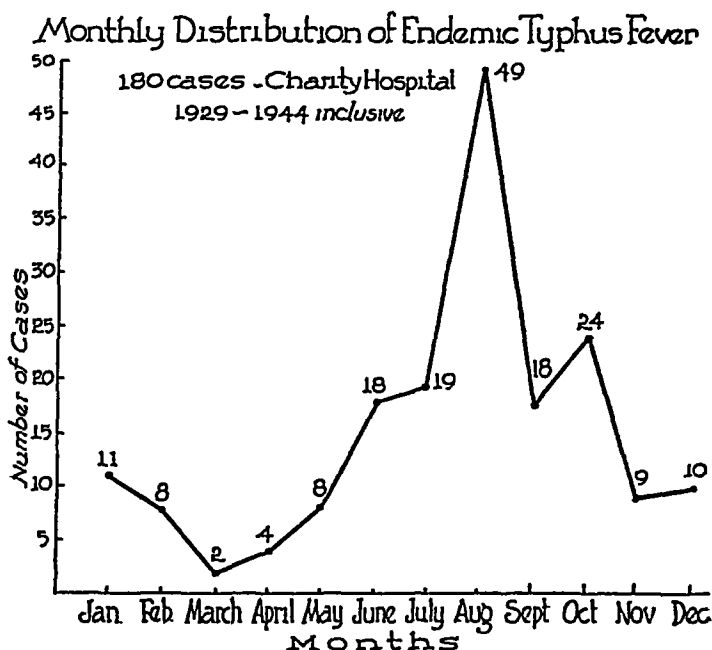


FIG 2 Monthly distribution of 180 cases of endemic (murine) typhus fever

As stated by others,<sup>20</sup> the highest incidence (figure 2) reaches its peak in the summer and early fall. Of our 180 cases, 128 (71.1 per cent) occurred from June to October inclusive, whereas the remaining 52 cases were scattered throughout the other seven months of the year.

*Racial Distribution* Of the 180 cases, 129 patients were white and 51 were negroes. Although this is not directly proportional to the admissions of white and colored patients during the same period, it is quite probable that failure to observe a skin rash on many of the negro patients resulted in an incorrect diagnosis in several instances. It does not, therefore, seem justified to assume any significant differences in racial susceptibility to the disease.

*Sex* There were 75 white male patients, 54 white females, 30 colored males and 21 colored females. An analysis of these data fails to reveal any significant differences in susceptibility in regard to sex, since the slight preponderance of male patients is probably due, at least in part, to occupational factors leading to contacts with the reservoirs of the disease.



*Age* The average age for our group of patients was 34.6 years, which is during the peak of active life, and was probably related to the contacts of the patients of our series in many instances. The youngest patient was a white female infant said to be 20 months of age, whereas the oldest patient in this series was a colored female of 67 years.

*Community Distribution* All of our patients, except one colored male who had just been released from prison in another state, were from Louisiana. This, of course, is due to the fact that the services of Charity Hospital are devoted almost exclusively to the citizenry of Louisiana and has no bearing, therefore, on the community distribution of endemic typhus elsewhere in the South. One hundred and twenty-five of our patients (69.44 per cent) were from New Orleans, whereas most of the remaining 55 were from rural communities. Fourteen (9.03 per cent) lived on farms.

*Occupational Factors* The occupational groups represented in this series varied greatly. Food-handlers, including 54 housewives, comprised the largest group, 80 patients (44.44 per cent), whereas the remainder included farmers, shipyard workers, common laborers, mechanics, carpenters, plasterers and several other occupational groups. Although employees working in food-handling establishments are quite likely to contract the disease, the occupation of an individual is not necessarily associated with its development.

*Contacts* Of our 180 patients, 123 (68.33 per cent) gave a suggestive history of contact. Sixteen of these had handled rats, four handled mice, and nine were of the opinion that they had recently been bitten by fleas. In each instance, a definite history of rats in the home or working environment was obtained. Thirty-four patients denied any contacts, while in 23 cases no historical data concerning contacts were available.

Dyer<sup>19</sup> has considered that endemic typhus may possibly have reservoirs in rodents other than the common rat. It is also generally thought that an infected rat flea may recover from the disease and harbor the *Rickettsiae* for four weeks or longer<sup>18</sup>. It would appear, therefore, that historical inquiry concerning exposure to animal contacts need not consider a wide variety of possibilities.

*Incubation Period* The incubation time is said to range from five to 15 days, the usual time falling between eight and 12 days<sup>18, 20</sup>. Although the majority of our patients gave a history of continued or multiple contacts, there were 29 who, according to historical data, had one exposure to rats, mice or fleas. The shortest incubation period of this group was apparently four days, but one patient became ill 15 days after his exposure. Among these 29 patients, the average time required for illness to occur after exposure was 10.4 days.

*Onset* Mild prodromal symptoms consisting of malaise, headache, cough, nausea, chest pain and coryza were each present in several of the 84 patients complaining of prodromata. The average duration of prodromata, which ranged from one to 10 days, was 2.7 days. The actual onset was sudden in 96 instances (53.33 per cent) and of these 79 suffered a chill in the

beginning Other common complaints associated with the onset of illness, sudden in nature, were severe headache, marked weakness or prostration, nausea and vomiting, pains in the chest, back, limbs and abdomen. Fever was nearly always present a few hours after the abrupt onset.

*Rash* The rash in endemic typhus is frequently not so pronounced as the exanthem associated with epidemic typhus, and may only comprise a few macules which disappear in two or three days. As may be seen from table 1, a rash was present in 115 cases, an incidence of 63.88 per cent. Only 10

TABLE I

| Race  | Rash Present | No Rash | Percentage with Rash |
|-------|--------------|---------|----------------------|
| White | 105          | 24      | 81.39                |
| Negro | 10           | 41      | 19.6                 |
| Total | 115          | 65      | 63.88                |

of 51 negroes were observed to have a skin rash, two of these papular, whereas the remainder were maculopapular and were seen on light-skinned negroes. The rash, as observed in white patients, when seen early, was usually a pinkish macular eruption, each macule ranging from 2 to 5 mm in diameter, which disappeared on pressure. This rash characteristically appeared on the fifth day of the disease, but was observed in some instances as early as the second or as late as the eighth day of illness. This exanthem usually originated on the trunk and spread peripherally to involve the limbs. The abdomen, chest, back, shoulders, arms and thighs were involved in the order of frequency, but the face was affected only thrice and the palms but twice. Scalp involvement was not observed. Itching was a rare complaint. The eruption was observed to fade less readily on pressure as it aged, and was more often papular, but in some instances disappeared completely in two or three days without leaving any tell-tale evidences. The duration of the rash, which varied between two and nine days, averaged six days, and usually had disappeared when defervescence occurred.

*Temperature* Seventy-nine of our patients suffered a transient chill at the onset, and 48 others experienced a chill within the first 48 hours. Following the actual onset, the fever characteristically began to rise rapidly or by successive steps, usually reaching its maximum by the end of the first week. The maximum temperature recordings in our series varied from 102° F to 106° F, but averaged 104° F. Of 127 patients who experienced chills some time during the course of their illness, 105 suffered multiple, transient chills, sometimes three or four within 24 hours. The chills recurred during a period between one and nine days in duration, with an average of 4.4 days. Only 16 of the 180 patients suffered no chills or chilly sensations during the course of their disease.

In our series of typhus patients, partial remissions of fever, usually in the mornings, were frequent during the second week of the disease. The average duration of the fever, which sometimes fell by crisis, but more characteristically by rapid lysis, was 15.6 days in this group excluding four pa-

tients with complicating diseases The duration varied from 12 days in one instance to 25 days in another The duration of fever in 85 per cent of our cases, however, was between 13 and 18 days Although defervescence by crisis was infrequently observed, an occasional case required as long as six days for lysis of the fever to occur, and the average number of days required for lysis was 3.5 days Following this fairly rapid drop in temperature, one or more transient temperature rises during the next two or three days were not unusual, but these were of no apparent clinical significance, and did not affect the general condition, which as a rule was suddenly and greatly improved

*Neuromuscular Manifestations* Headache was usually the most prominent neurologic symptom, being present in 154 patients (85 per cent) of this series The headache was not persistent in localization, was usually severe and not easily relieved, and often persisted throughout the illness Although not so predominant a characteristic as in epidemic typhus, varying degrees of mental disturbance which varied from coma, stupor or lethargy, to confusion and delirium were observed Stupor, seen in 28 instances (15.55 per cent), was the most frequent manifestation while delirium or excitement was seen 12 times and coma was present in only three cases Nuchal rigidity was present in 10 patients Despite the cerebral changes associated with typhus fever, which are similar to those seen in the virus encephalitides, reflex abnormalities were not present Neurologic manifestations so severe as to suggest the necessity for lumbar puncture were present 20 times These evidences of nervous system involvement usually cleared up rapidly with the fall in temperature associated with recovery

Generalized muscular aches and pains were a prominent feature in 160 instances, back pain was present 138 times, marked weakness usually without actual prostration 130 times, and neck pains in 52 cases These complaints were usually manifest early in the disease and frequently persisted until defervescence occurred

*Special Senses* Aching and soreness of the eye muscles occurred 20 times, an incidence of 11.11 per cent, while photophobia was a complaint of 30 patients (16.67 per cent) Conjunctival injection, varying in duration and severity, was present 92 times (51.11 per cent) Transient partial deafness was a complaint of five patients and tinnitus was noticed by 12 patients, five of whom received quinine therapy before entering the hospital

*Respiratory Manifestations* Some evidences of respiratory tract involvement were present in over half of this group of patients, but were not so prominent a feature as in Maxcy's series<sup>11</sup> of 114 cases A characteristic short, hacking cough was present in 106 of our patients (figure 3), an incidence of 58.88 per cent Most often the cough was non-productive, but mucopurulent sputum was raised by several, and blood-tinged sputum was produced nine times, being present in five patients with clinical and roentgenologic evidences of bronchopneumonia Coryza, sore throat and chest pain were also frequent complaints The most frequent respiratory sign

found was the presence of râles, usually moist, at the base of the lungs. These râles were undoubtedly a manifestation of bronchitis or bronchopneumonia in some cases, but may have been due to cardiac weakness and resulting pulmonary congestion in many others. As shown in figure 3, cyanosis was present eight times (4.44 per cent) and a friction rub was heard but once (0.55 per cent). Respirations were somewhat increased, maximum respirations recorded averaging about 30 per minute in uncomplicated cases, and markedly increased (40 or more in 10 cases) when bronchopneumonia developed.

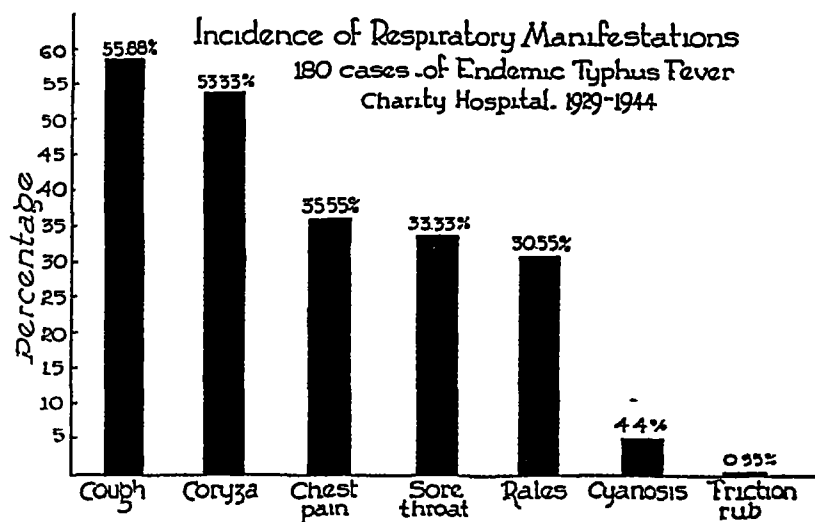


FIG 3 Incidence of respiratory manifestations of 180 cases of endemic (murine) typhus fever

The symptoms and signs of respiratory tract involvement were present sufficiently often to have 100 of the patients (55.55 per cent) subjected to roentgenographic examinations of the chest, several of these having two or more such examinations. Of these 100 patients, roentgenograms were considered entirely normal in 69 per cent, whereas four showed evidences of pulmonary tuberculosis which was thought to be inactive. The remaining 27 roentgenograms included 18 which were interpreted as showing signs of peribronchial thickening or hilar enlargement, while the other nine, 5 per cent of the entire series, revealed the presence of bronchopneumonia.

**Cardiovascular Manifestations** Symptoms referable to the cardiovascular system were surprisingly few when one considers that the pathologic process of typhus is based on acute lesions of the blood vessels. Lowering of the diastolic blood pressure as much as 20 mm of mercury was observed in several severe cases with evidences of marked cardiac weakness. Cardiac failure necessitating the utilization of digitalis occurred twice: one of the patients having hypertensive heart disease, and the other, 67 years of age, apparently suffering with arteriosclerotic heart disease. Although no cardiac

fatalities were observed in our series, an occasional sudden death in patients not appearing acutely ill has been reported <sup>11</sup>

Venous thrombosis, occurring in the right cephalic vein, was witnessed once, and surprisingly enough did not follow the administration of intravenous medications. The pulse was subject to variations ranging between 80 and 160, the increase in rate being generally proportional to the degree of fever. The average maximum pulse rate in this series of patients was approximately 120 per minute. A dicrotic pulse was said to be present six times, an incidence of 3.33 per cent.

*Gastrointestinal Manifestations* Complaints referable to the gastrointestinal tract, although quite troublesome at times, were usually of no major importance. Nausea, vomiting, or both, were present in 65 cases (36.11 per cent) and were usually more pronounced at the onset. Diarrhea varying a great deal in severity was a factor in 19 instances (10.55 per cent) whereas constipation, frequently troublesome throughout the disease, was present in 48 (26.67 per cent). Some degree of abdominal pain was present in 39 patients, an incidence of 21.67 per cent. Distention was observed in 17 patients (9.44 per cent) and tenderness on abdominal palpation was elicited on 13 occasions. The liver edge was palpable in 12 (6.67 per cent), and suspicions that jaundice was present led to icterus index determinations in 11 cases, only one of these being abnormal.

The spleen, which characteristically enlarged somewhat early in the disease, was palpable in 48 and questionably palpable in 10 others, making 58 (32.22 per cent) with spleens probably palpable. In almost every case the spleen rapidly regressed in size as clinical improvement became apparent.

*Genitourinary Manifestations* Abnormalities referable to the genitourinary tract were not prominent. Nevertheless, back pains, a prominent feature of the disease when associated with chills and transient albuminuria, were responsible for a presumptive diagnosis of pyelonephritis in six cases.

#### LABORATORY FINDINGS

As will be shown later, about 75 per cent of these patients entered the hospital with diagnoses other than typhus fever. Consequently, this group of patients was subjected to a large number of laboratory tests. Blood cultures, consistently negative, were obtained from 137 of these patients (76.11 per cent), blood smears in a search for malaria were done 49 times (27.22 per cent), urine cultures in about one-half, spinal fluid surveys 20 times, blood urea nitrogen determinations 51 times, and blood glucose, icterus index, serum protein and other laboratory determinations were each done in several instances.

*Weil-Felix Reaction* The agglutination of certain strains of the *Proteus* bacillus, called OX<sub>10</sub> and OX<sub>2</sub>, by the blood serum of the patient is known as the Weil-Felix reaction <sup>21</sup>. A total of 448 such tests was made during the illness of our 180 patients (figure 4), and it was found that the agglutinins

characteristically appeared at the end of the first week or during the second week of the disease. No tests were positive before the fifth day of illness, three of 20 being positive on that day. It was found that 95 tests failed to reveal the presence of agglutinins, the average duration of disease at the time of these examinations being 6.8 days. The average time required for the appearance of agglutinins in the titer of 1:80 was 8.5 days, 1:160 was 10.5 days, 1:320 was 11.4 days, 1:640 was 13.3 days, 1:1280 was 15.9 days, and 16.4 and 19.5 days respectively were the average duration before the appearance of agglutinins in the titers of 1:2560 and 1:5120.

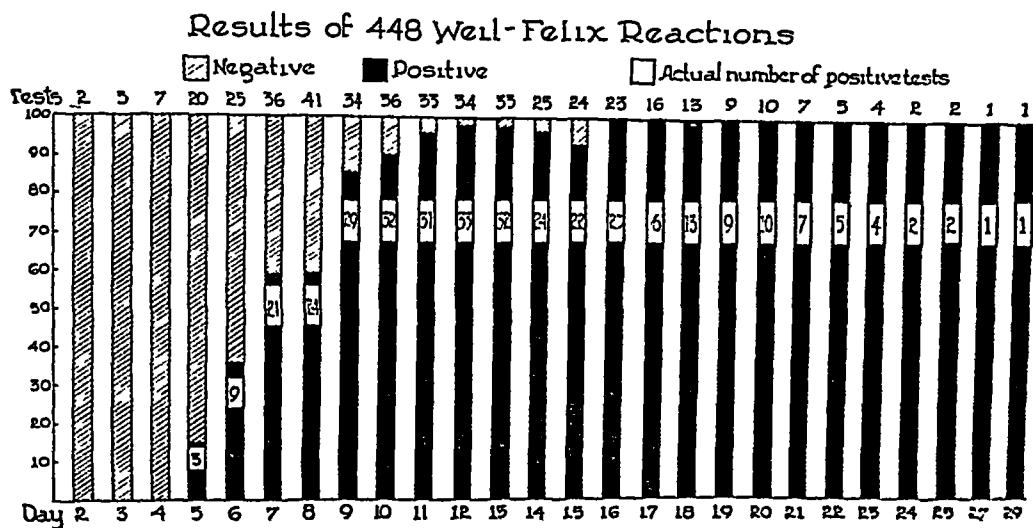


FIG. 4. Results of 448 Weil-Felix determinations. The figures at the top of each column represent the actual number of determinations performed on that particular day. The figures inserted in the heavily shaded part of each column denote the actual number of positive reactions while the percentage values are determined by the ordinates of the graph.

Although most of these cases were undoubtedly examples of endemic typhus, it is now known that Rocky Mountain spotted fever also shows a positive Weil-Felix reaction in high titers and consequently this reaction is of no practical value in differentiating between typhus and spotted fever. Recently, however, the complement fixation phenomenon, which becomes positive during the second week of the disease and may remain positive for many years, has been utilized in differentiating typhus and spotted fever. This phenomenon unfortunately has been utilized in few of our cases, but in one instance was responsible for establishing the diagnosis of spotted fever, the Rickettsiae of spotted fever being used as an antigen.

**Blood Picture.** Although cellular examination of the blood is none too characteristic, it was found from an analysis of 218 white blood cell counts from our patients (figure 5) that a mild leukopenia is usually seen during the first week of the disease, and that the increase in white cells during the second week results in a mild leukocytosis. Counts ranging from 2,500 to 15,000 cells are occasionally seen in uncomplicated cases. The differential white

cell count usually fell within normal limits, and the red blood cell and hemoglobin values were apparently not affected by the disease

*Urine* Excluding two examples of chronic renal disease, the only abnormal urinary finding observed was albuminuria, which was present 30 times (17.04 per cent). This albuminuria, which usually appeared during the first week of the disease, consistently cleared up with convalescence

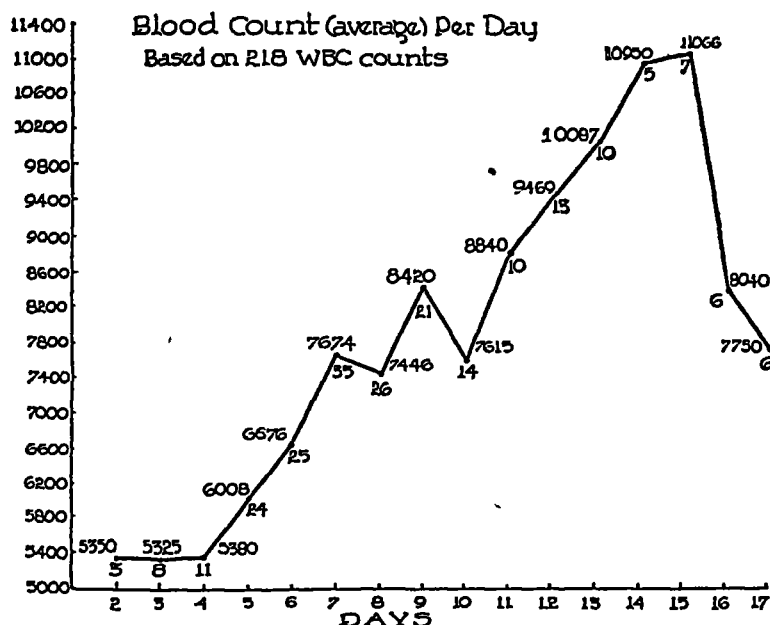


FIG 5 The average values of 218 white blood cell counts performed on various days of illness. The figures below the curve represent the actual number of determinations on that particular day with the averaged value designated immediately above the curve

*Blood Serology* Serologic examinations were recorded in 172 instances. Four of these demonstrated positive Kline and Kolmer tests during their febrile period, these reactions becoming negative and remaining so after defervescence occurred. Thirteen patients were found to have consistently positive serologic evidences of syphilis.

#### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

When present in epidemic form, little difficulty should be experienced in diagnosing typhus fever, but sporadic cases of the endemic type may prove more troublesome. When one bears in mind certain characteristics of the disease, it is frequently possible to entertain a presumptive diagnosis of typhus fever, especially when a contact history is obtained. An acute infectious disease, characterized by a fairly sudden onset and continuous fever of about two weeks terminating by rapid lysis is usually seen. Although a presumptive diagnosis may occasionally be made on the basis of the early symptomatology, considerable aid is obtained with the appearance of a macular rash after about five days which, in many cases, has a fairly characteristic appearance and distribution.

The routine laboratory findings, other than the Weil-Felix reaction, are not diagnostic. A mild leukopenia is usually present early in the disease, and albuminuria is observed in a small percentage of the cases. The Weil-Felix reaction, although of great diagnostic value, usually does not appear until the seventh day or later, and does not prove helpful in differentiating between endemic typhus and Rocky Mountain spotted fever.

The complement fixation phenomenon, only recently used in differentiating rickettsial diseases, which utilizes the Rickettsiae of endemic typhus fever, characteristically becomes positive during the second week of the disease, and may remain positive for many years. This test is of definite value, especially in areas where endemic typhus and spotted fever both occur.

In experienced hands, biopsies of the skin are valuable diagnostic aids. Suitable specimens may be obtained by widely excising a clearly demarcated, macular lesion, which should be fixed in Regaud's fluid and stained by the Giemsa method.<sup>16</sup> In typhus, Rickettsiae, if present, will be found only in the endothelial cells, whereas in Rocky Mountain spotted fever the Rickettsiae will be seen in the smooth muscle cells of the arteriolar walls.

Inoculation of male guinea-pigs and white male rats may be necessary when doubtful cases are encountered. In these instances cross immunity tests may be done. Six c.c. of blood drawn from the patient during the first week of the disease are injected intraperitoneally into each of several guinea-pigs and rats. An incubation period ranging from four to 12 days should elapse, the febrile course being observed during this period. Scrotal reactions in either animal and the development of a heavy exudate with abundance of Rickettsiae is typical of endemic typhus. Such a reaction is conclusive in the rat. Smears of scrotal cells in typhus reveal massive growth of the Rickettsiae in the cytoplasm without invasion of the nuclei. In contradistinction, smears from scrotal cells in spotted fever usually reveal a few large widely disseminated Rickettsiae in the cytoplasm, and frequent invasion of the nuclear substance. When satisfactory scrotal reactions are not obtained, immunity tests with known strains of typhus and spotted fever will usually complete the diagnosis. When an occasional atypical strain is encountered, the results of these tests may not be decisive. Under such circumstances, tissue cultures may be helpful, the extensive intranuclear growth in spotted fever is clearly seen, whereas the typhus organisms grow extensively in the cytoplasm.

Although in areas endemic to both typhus and Rocky Mountain spotted fever the final diagnosis is usually concerned with differentiating these two diseases, a large number of diseases was considered in the differential diagnosis of the 180 cases in our series. Forty-four of these cases (24.4 per cent) entered the hospital with a presumptive diagnosis of typhus fever. Other admission diagnoses are tabulated below.



*Common Diagnoses*

|               |                 |
|---------------|-----------------|
| Typhoid fever | Pyelonephritis  |
| Pneumonia     | Virus pneumonia |
| Malaria       | Measles         |
| Influenza     | Drug rash       |

*Less Common Diagnoses*

|                                 |                     |
|---------------------------------|---------------------|
| Secondary syphilis              | Pharyngitis         |
| Undulant fever                  | Bronchitis          |
| Arsenical hepatitis             | Sinusitis           |
| Subacute bacterial endocarditis | Encephalitis        |
| Cholecystitis                   | Cerebral concussion |
| Central nervous system syphilis | Infectious diarrhea |
| Intestinal obstruction          | Polomyelitis        |
| Pelvic inflammatory disease     | Plumbism            |
| Meningococcemia                 | Tuberculosis        |

Although it is practically impossible to differentiate early typhus from many of these diseases, the appearance of a rash, characteristic febrile response, absence of leukocytosis, and appropriate laboratory procedures serve to eliminate most of them from the list of diagnostic possibilities. Typhoid fever, the most troublesome to differentiate, may be ruled out by blood culture, negative Widal reaction, and the different appearance and distribution of the rash. The rose spots of typhoid characteristically appear in crops, and are usually less numerous than are typhus lesions. Malaria may be eliminated by examination of blood smears, whereas the pneumonias should be excluded by roentgenologic studies of the chest. An adequate survey of the urinary tract is essential when considering pyelonephritis, while influenza and measles seldom prove troublesome for long. Drug rash, since the introduction of the sulfonamide preparations, may prove difficult to exclude, especially when a history of recent sulfonamide therapy is obtained, but discontinuing the drug frequently proves helpful if other toxic manifestations such as suppression of the urinary output or hematuria are absent.

*COURSE*

Most of the patients entered the hospital after one week of illness, but admissions varied from the first day until convalescence. The average duration of hospitalization was 15.7 days, whereas an average of 23 days elapsed between the onset at home and the day of hospital discharge. The febrile response and the rash have been described in detail. The headache as well as various other aches and pains persisted in many cases, but always disappeared before the temperature became normal.

### COMPLICATIONS AND SEQUELAE

Bronchopneumonia, occurring in nine of these patients, was the most common complication. Thrombosis of the right cephalic vein, possibly of *no clinical significance* in regard to the disease, was observed once. Only three of the patients, all in the older age group, developed bed sores. Inadequate data concerning this series of patients after hospital discharge prevent any worthwhile conclusions concerning sequelae, but some writers are of the opinion that there are no true sequelae.<sup>15</sup>

### PROGNOSIS

The mortality from endemic typhus in the United States as a whole is usually given as about 1 per cent.<sup>15</sup> Most of these deaths are said to occur in the aged. In contradistinction, the case-fatality rate during different epidemics of louse-borne typhus varies from 20 to 60 per cent.<sup>16</sup> There were no deaths in our series of 180 cases.

### TREATMENT

There is no specific treatment of established value. Symptomatic and supportive measures, designed to maintain the strength of the patient which included strict bed rest, good nursing care, maintenance of fluid balance and a liquid or soft nourishing diet with supplementary vitamins, were the basis of the therapeutic regimen in most of our cases. Occasionally a stomach tube was necessary in order to administer the necessary fluid and nutritional requirements. Digitalis was administered twice in cases showing evidences of cardiac failure. Constipation was best controlled by using enemas, whereas adequate nursing care aided in preventing bed sores. Codeine and aspirin were frequently necessary for the control of the headache, however, in many instances only minimal relief was obtained. Temperature-reducing measures such as alcohol and cold water sponge baths were employed freely. Quinine sulfate, usually 10 grains three or four times daily, was given to several of the patients with only transient effects on the febrile course of the disease. Each of the sulfonamide derivatives except sulfamerazine was given in full dosage to several of these patients before the correct diagnosis was established, the results being uniformly unsatisfactory. One patient, a white female of 28 years, received more than 700 000 units of penicillin before typhus was suspected, but no appreciable change in the course of the disease was noted. All the patients, except two deserting at the time of defervescence, were kept in bed until convalescence was well established.

From experimental work by Pinkerton and Bessey<sup>2</sup> which shows that riboflavin deficiency leads to a striking and apparently specific loss of resistance to endemic typhus in the rat it appears that the injection of crystalline riboflavin in man is perhaps indicated, particularly when a history of an inadequate diet is obtained. Pinkerton<sup>17</sup> has also found that the with-

holding of food following inoculation causes marked loss of resistance to experimental typhus in the guinea-pig. These observations lend emphasis to the importance of nutrition in typhus.

Recent studies by Woodward and Bland,<sup>26</sup> based on severe epidemic typhus in French Morocco, indicate that the circulatory collapse in typhus is mainly peripheral in origin. They demonstrated reductions in the blood volume and in blood proteins, especially albumin, and other alterations, all attributable to the vascular lesions of typhus and increased capillary permeability. They emphasize the importance of general supportive measures to restore the volume and quality of the blood. A more recent report by Hatrell and his co-workers<sup>27</sup> on the treatment of Rocky Mountain spotted fever indicates similar findings. Thus it would appear that supportive measures should be utilized more in the treatment of conditions caused by the specific *Rickettsiae*.

Serum preparations are apparently of questionable value. There is experimental evidence indicating that the various sulfonamide preparations are of no value in treating typhus fever, whereas available data suggest in fact that these drugs, in experimental typhus, seem to have a deleterious effect.<sup>28, 29</sup> Penicillin has been found by Pinkerton and his co-workers<sup>30, 31</sup> to exert a beneficial effect in experimental typhus, both in mice and the infected yolk sacs of developing chick embryos. Penicillin has not yet been subjected to an adequate clinical trial, however, and it is not known whether penicillin, given early and in large amounts, will affect the course of endemic or epidemic typhus. As suggested by Yeomans and co-workers,<sup>32</sup> this therapeutic agent would seem indicated when evidences of secondary infection appear, especially since sulfonamide derivatives are thought to be detrimental in rickettsial diseases.

A recent report by Yeomans and his associates<sup>32</sup> has indicated that para-aminobenzoic acid lessens the severity and shortens the duration of louse-borne typhus. Their study, based on 20 treated cases and 44 "untreated cases," indicates that when administered properly no undesirable effects are to be expected except a tendency to develop a low white blood cell count. Although further information is needed, this therapeutic substance may also prove valuable in lessening the severity and duration of endemic typhus.

## PREVENTION

Since the rat is the reservoir, the control of endemic typhus fever should be based on the control of the rat population. This is best accomplished by poisoning and trapping, the rat-proofing of buildings, and the disposition of garbage beyond access to rats. Of these measures, rat-proofing is the only one that may be considered as of some permanent value. Unless supplemented by this measure, trapping and poisoning must be continuous to be of any practical value.

Vaccines utilizing technics employing living cells as a medium have been prepared against endemic typhus. Immunization programs are not generally advocated, however, since the mortality rate is low and the disease occurs sporadically, usually showing little tendency to become epidemic. Dyer<sup>13</sup> has suggested that the vaccine might be used to advantage in the protection of those employed in food-handling establishments, but points out that one is not justified in enabling the management of such an establishment to maintain rat harborage.

### SUMMARY

We have reported the clinical observations of 180 cases of endemic (murine) typhus fever occurring in the past 16 years at Charity Hospital of Louisiana at New Orleans. Almost one half of these cases have been observed, however, in the past three years and this and other data lend support to an increasing incidence of typhus fever in the southern United States. The clinical picture, diagnosis and treatment of the disease have been discussed in detail.

### BIBLIOGRAPHY

- 1 MUSSER, J. H. Typhus fever in Louisiana, *New Orleans Med and Surg Jr*, 1930, **LXXXII**, 473.
- 2 JOSEPH, C. Typhus fever in Charity Hospital, *New Orleans Med and Surg Jr* 1940, **XCIII**, 39.
- 3 GERHARD, W. W. On the typhus fever which occurred at Philadelphia in the spring and summer of 1836, *Am Jr Med Sci*, 1837, **XX**, 289.
- 4 BRILL, N. E. An acute infectious disease of unknown origin, *Am Jr Med Sci* 1910, **CXXXIX**, 484.
- 5 ZINSSER, H. Epidemiology of Rickettsial disease. In *Harvard School of Public Health Virus and Rickettsial diseases*, 1940, Harvard University Press, Cambridge.
- 6 PAULLIN, J. E. Typhus fever with a report of cases, *South Med Jr*, 1913 **VI**, 36.
- 7 NEWELL, L. B., and ALLAN, W. Typhus fever, a report of four cases, *South Med Jr*, 1914, **VII**, 564.
- 8 MCNEIL, H. L. Endemic typhus fever in south Texas, *Texas State Jr Med*, 1916, **VII**, 188.
- 9 ALLAN, W. Endemic typhus fever in North Carolina, *South Med and Surg* 1923, **LXXXV**, 65.
- 10 MACCY, K. F., and HAVENS, L. C. A series of cases giving a positive Weil-Felix reaction, *Am Jr Trop Med*, 1923, **III**, 495.
- 11 MACCY, K. F. Clinical observations on endemic typhus (Brill's disease) in southern United States, *Pub Health Rep*, 1926, **VI**, 1213.
- 12 MACCY, K. F. An epidemiological study of endemic typhus (Brill's disease) in southeastern United States, *Pub Health Rep* 1926 **VI**, 2967.
- 13 DYER, R. E., CORDER, E. T., LILLIE, R. D., RUMERICH, A., and BARTER, I. F. Experimental transmission of endemic typhus fever of the United States by the rat flea, *Pub Health Rep*, 1931, **XLVI**, 2415.
- 14 MOOSER, H. Reaction of guinea-pigs to Mexican typhus (Tihardillo). *Jr Am Med Assoc*, 1928, **XCI**, 19.
- 15 PINKERTON, H. in BERKOVITZ, Z. F. *Clinical tropical medicine* 1944 P. B. Hoeber, New York.

- 16 DYER, R E Typhus fever, *Med Clin N Am*, 1943, xxvii, 775
- 17 COX, H R Use of yolk sac of developing chick embryo as medium for growing Rickettsiae of Rocky Mountain spotted fever and typhus groups, *Pub Health Rep*, 1938, liii, 2241
- 18 SPINK, W W In MUSSER, J H *Internal Medicine*, fourth edition, 1945, Lea and Febiger, Philadelphia
19. FRAENKEL, E Ueber Fleckfieber und Roseola, *Munchen med Wehnschr*, 1914, lxi, 57
- 20 DYER, R E The rickettsial diseases, *Jr Am Med Assoc*, 1944, cxxiv, 1165
- 21 FELIX, A Serological types of typhus virus and corresponding types of Proteus, *Trans Royal Soc Trop Med*, 1933, xxviii, 147
- 22 BENGSTON, I A, and TOPPING, N H The specificity of the complement fixation test in endemic typhus fever using a rickettsial antigen, *Pub Health Rep*, 1941, lvi, 1723
- 23 PLOTZ, H, and WERTMAN, K The use of complement fixation test in Rocky Mountain spotted fever, *Science*, 1942, lcv, 441
- 24 PULLEN, R L, SODEMAN, W A, and FELKNOR, G E Rocky Mountain spotted fever Differentiation from typhus fever and report of a case, *New Orleans Med and Surg Jr*, 1945, xcvi, 359
- 25 PINKERTON, H, and BESSEY, O A The loss of resistance in murine typhus infection resulting from riboflavin deficiency in rats, *Science*, 1939, lxxxix, 368
- 26 WOODWARD, T E, in collaboration with BLAND, E F Clinical observations in typhus fever, with special reference to the cardiovascular system, *Jr Am Med Assoc*, 1944, cxxvi, 287
- 27 HARRELL, G T, VENNING, W, and WOLFF, W A The treatment of Rocky Mountain spotted fever, *Jr Am Med Assoc*, 1944, cxxvi, 929
- 28 TOPPING, N H Experimental Rocky Mountain spotted fever and endemic typhus treated with prontosil and sulphapyridine, *Pub Health Rep*, 1939, liv, 1143
- 29 SNYDER, J C, MAIER, J, and ANDERSON, C R Report to the Division of Medical Sciences, National Research Council, Dec 26, 1942
- 30 GRIEFF, D, and PINKERTON, H Inhibition of growth of typhus Rickettsiae in the yolk sac by penicillin, *Proc Soc Exper Biol and Med*, 1944, lv, 116
- 31 MORAGUES, V, PINKERTON, H, and GRIEFF, D Therapeutic effectiveness of penicillin in experimental murine typhus infection in mice, *Jr Exper Med*, 1944, lxxxix, 431
- 32 YOMANS, A, SNYDER, J C, MURRAY, E S, ZARAFONETIS, C J D, and ECKE, R S The therapeutic effect of para-aminobenzoic acid in louse-borne typhus fever, *Jr Am Med Assoc*, 1944, cxxvi, 349

# THE USE OF THIOURACIL IN THE TREATMENT OF PATIENTS WITH HYPERTHYROIDISM

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## HISTORICAL REVIEW

THE origin of the use of thiouracil in the treatment of hyperthyroidism stems from the past studies of the mechanism of the production of experimental goiter. During the course of these studies in which the rôle of iodine in the production of simple goiter was convincingly demonstrated, many interesting facts were unearthed that were to be of striking importance in the development of the rationale for the use of thiourea derivatives in the treatment of hyperthyroidism.

In 1928, Chesney and his co-workers<sup>1</sup> noted the development of goiter in their stock rabbits fed on a cabbage diet. The thyroid glands of these animals were found to be enlarged, and microscopically they showed considerable hyperplasia with no tendency to colloid formation. This development was accompanied by a decrease in the production of body heat, the heat production varying inversely with the size of the thyroid. Iodine administered to the goiterous animal resulted in a rise in metabolic rate and a fall in body weight. It brought about, however, involution of the hyperplastic gland.

In 1930, Webster and Chesney<sup>2</sup> demonstrated that the administration of iodine in sufficient quantities would protect rabbits against the goitrogenic effect of the cabbage diet. Meanwhile, Marine and his co-workers<sup>3</sup> showed that other members of the Brassica group were also goitrogenic. The goitrogenic effect, however, was inversely proportional to its iodine content. It was, therefore, presumed that cabbage contained an agent that reduced the effective thyroxin and iodine content of the thyroids of rabbits. This resulted in hyperplasia of the gland.

Since the most important chemical constituents of the Brassicae were mustard oils, the effect of these isothiocyanates and their cyanide precursors were investigated. With acetonitrile, and other related compounds, Marine<sup>4</sup> was able to produce hyperplasia of the thyroids, and, in some animals, exophthalmos.

Soy bean flour was also demonstrated to be goitrogenic in rats.<sup>5</sup> The thyroid became hyperplastic with little or no colloid. The basal metabolic rate remained unaltered. The development of goiter by this means could similarly be prevented by the use of iodine, the minimum iodine requirement

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From the Medical Services of The Mount Sinai Hospital, New York City.  
The Thiouracil was furnished by Lederle Laboratories, Inc., Pearl River, N Y.

being twice that necessary in normal rats. It was presumed, since soy beans are rich in cyanogens, that these latter were the goitrogenic agents.<sup>7</sup>

That the cyanide derivatives may have an importance in clinical medicine is emphasized by the fact that the development of goiter is not infrequent in hypertensive patients receiving thiocyanates<sup>8,9</sup>. Means and his group reported the results observed in a case of hypertension treated with thiocyanates. With the development of goiter, the basal metabolic rate fell to — 17 per cent, lid lag and exophthalmos developed, and the plasma iodine content fell to myxedematous levels. Biopsy of the thyroid revealed extreme hyperplasia and vascularity. Following cessation of therapy, the basal metabolic rate and the plasma iodine level returned to normal, while the thyroid became considerably smaller.

In 1941, Richter and Clisby,<sup>10,11</sup> while studying the effects of phenylthiocarbamide, found that rats fed this drug developed goiter with marked hyperplasia of the thyroid gland. No exophthalmos was noted. At about the same time (1941), Kennedy and his group<sup>12</sup> studied the goitrogenic agents in Brassica seeds. They found that the diet was markedly goitrogenic in rats, but unlike soy bean and cabbage diets, large doses of iodine afforded only a minimal protection against the resulting hyperplasia and hypertrophy of the thyroid.

Marked changes in the basophile cells of the pituitary gland were noted to occur in rats that had been fed soy bean flour and were similarly observed following thyroidectomy. Giesbach<sup>12</sup> found that the changes in the pituitary in rats fed rape seed reflected the changes in the thyroid, the basophiles increasing in number as the thyroid underwent hyperplasia, whereas the acidophilic elements accumulated when colloid storage occurred. It was concluded that the basophile changes coincided with an increased secretion of thyrotropic hormone. Kennedy and his co-workers<sup>12</sup> were able to show that an intact hypophysis was essential for the production of thyroid hyperplasia. Hyperplasia produced by the diet regressed after hypophysectomy, while colloid formation after hypophysectomy was not prevented by the goitrogenic diet.

Almost simultaneously, the MacKenzies and McCollum,<sup>13</sup> studying the effect of sulfaguanidine on the coliform bacteria in rats, noted the development of thyroid hyperplasia and hypertrophy following the use of this drug. Similar changes were noted to occur with the use of sulfanilamide and thiourea.<sup>14</sup>

Kennedy<sup>15</sup> attempted to isolate the goitrogenic agent in rape seed, and suggested that it might be a derivative of thiourea. Allylthiourea was tested and found to produce goiter in rats, with changes in the thyroid and pituitary glands similar to those seen after the ingestion of rape seed. No toxic effects were encountered.

In 1943, the MacKenzies<sup>16</sup> and Astwood<sup>17</sup> simultaneously published their results on the mechanism of the production of goiter by the sulfon-

amides and thiourea derivatives. It was shown that the thyroid underwent marked hyperplasia, that the basal metabolic rate fell, that changes like those following thyroidectomy occurred in the anterior lobe of the pituitary, and that iodine was of no avail in counteracting these changes. They could be prevented, however, by thyroid extract or by hypophysectomy. The occurrence of a lower basal oxygen consumption, the decrease in food intake, and the diminished rate of growth and development suggested a hypothyroid state.

Astwood<sup>18</sup> studied a large group of compounds including the sulfonamides, thiourea, and cyanides in an attempt to determine the chemical grouping responsible for the action, as well as to determine the agent with the greatest potency and least toxicity. He found that two classes of substances were active, derivatives of thiourea, of which 2-thiouracil was the most effective, and certain derivatives of aniline dyes, including the sulfonamides. Thiocyanates were found to be active only in the absence of iodine, whereas organic cyanides were without effect.

In 1943, Astwood<sup>19</sup> reported preliminary studies on the use of thiourea and thiouracil in the treatment of hyperthyroidism. Many reports have appeared since then dealing with the use and toxic effects of these compounds<sup>20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 47, 48</sup>

### MECHANISM OF ACTION

In experimental animals, the administration of thiourea and related compounds produces a fall in the basal metabolic rate, hyperplasia of the thyroid, the appearance of "thyroidectomy cells" in the anterior lobe of the hypophysis, lessens food intake and causes subnormal growth and development.<sup>34, 49</sup> The experimental evidence would suggest that these substances result in a decrease in the production of thyroid hormone, possibly by interfering with the iodination of protein. It is this reduction in the formation of thyroxine which causes a fall in the basal metabolic rate and the disappearance of the other signs and symptoms of hyperthyroidism noted clinically. The reduction in the amount of circulating thyroid hormone produces a compensatory increase in the formation of thyrotropic factor by the anterior pituitary lobe. The thyrotropic factor, in turn, induces the hyperplasia of the thyroid.

### CLINICAL RESULTS

We have employed thiouracil in the treatment of 51 patients with hyperthyroidism and in three patients with non-toxic goiter. This last group was admitted to the hospital for cosmetic thyroidectomies and thiouracil was employed in order to study the effect of this drug on the histology of the thyroid.

The patients were hospitalized for a period of four to six weeks and were subsequently followed in the Out-Patient Clinic for the duration of the



study During their stay in the hospital, in addition to frequent basal metabolic rate determinations, careful studies of renal and hepatic function were conducted both at the beginning of thiouracil therapy and just before discharge from the hospital Complete blood counts were performed twice a week This procedure was continued after discharge from the hospital to the Out-Patient Clinic Sternal marrow aspirations were performed several times on each patient during the period of observation Blood cholesterol determinations, circulation time, electrocardiographic tracings, neck size and measurements of the degree of exophthalmos were determined once a week while the patient was in the hospital

Liver function studies performed on each patient included the determination of the icteric index, cephalin flocculation test, galactose tolerance test, and determination of urinary urobilinogen Renal function studies included gross and microscopic examination of the urine, determination of urine albumin and urine concentration tests

The dosage employed varied from 0.4 gram to 1.0 gram daily in divided doses for the first four weeks during the patient's stay in the hospital When the patient was discharged for care in the Out-Patient Department, the amount of the drug was reduced to 0.1 or 0.2 gram daily thereafter It has been our impression in general that most patients do better when the larger doses are employed In some instances we have obtained equally satisfactory results where smaller amounts of the drug were used The frequency and severity of the toxic reactions are apparently independent of the dosage of the drug employed

*The Effect of Thiouracil Therapy on the Basal Metabolic Rate, Pulse, and Weight* In all of the patients in Group A (chart 1) there occurred a fall in

#### CHART I

##### Summary of Cases Studied

- A Hyperthyroidism treated successfully with thiouracil
  - 1 Primary hyperthyroidism—29 cases
  - 2 Recurrent hyperthyroidism—4 cases
- B Hyperthyroidism Lack of response to thiouracil—4 cases
- C Hyperthyroidism Cessation of therapy due to toxic reactions—11 cases
- D. Hyperthyroidism Prepared for operation with thiouracil—3 cases
- E. Non-toxic goiter Prepared for operation with thiouracil—3 cases

the basal metabolic rate, a gain in weight, and a slowing of the pulse Subjective improvement in symptoms was usually the earliest evidence of a beneficial effect This was noted toward the end of the first week or early in the second week of therapy Some reduction in the basal metabolic rate frequently occurred within one week, but a definitely significant fall was generally not observed until the second or third week, and in a few instances the lag was slightly longer Figure 1 illustrates the fall in the basal metabolic rate plotted against the time, in 10 instances A gain in weight and fall in pulse rate accompanied the reduction in basal metabolic rate

One of the important factors causing a delay in response in the basal metabolic rate was the previous administration of iodine, although this is not always true. Thus in case 5, who had been receiving Lugol's solution for five months before treatment with thiouracil there was a fall in the basal metabolic rate noted in two weeks with a progressive fall noticeable thereafter, especially during the fourth week and later (figure 1). How-

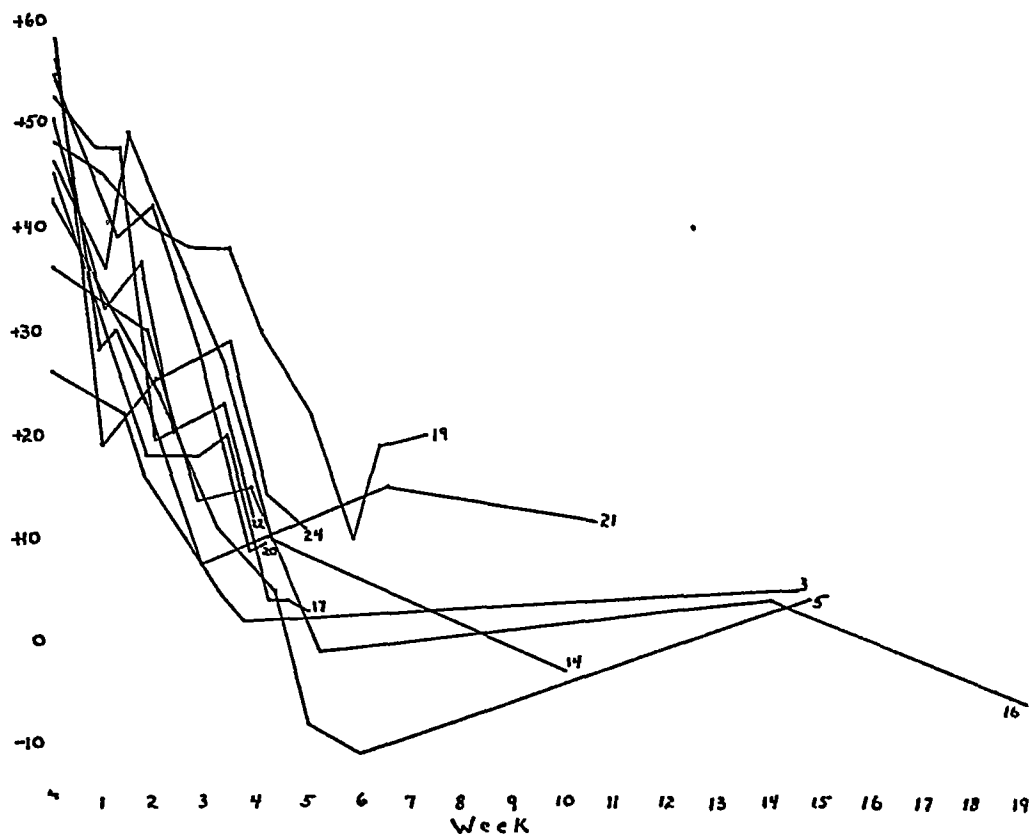


FIG 1 The BMR-time relationship of 10 selected cases on thiouracil therapy in Group A. The numbers refer to the cases (see text).

ever, in a second instance (case 2, figure 2) the patient had received Lugol's solution for eight months, and a moderate fall in the basal metabolic rate was noted in two weeks, but then a plateau ensued and a further fall was noted in the Follow-Up Clinic seven weeks after the onset of therapy. In a third patient (case 13) who had received Lugol's solution for three months, no effect on the basal metabolic rate was noted in the hospital after 18 days of therapy. No further determination of the basal metabolic rate was made until eight weeks after the onset of therapy, at which time there was a considerable drop. The failure of response in two cases to be discussed later, cases 38 and 39, may have been due in part to the previous use of iodine.

These effects are what one would expect from a consideration of the results of animal experiments, and are in conformity with the findings of most other observers. The object of treatment with thiouracil is either to treat the patient with hyperthyroidism until a natural remission occurs, or to continue such treatment until exhaustion atrophy sets in and permanent cure results. The intensity and duration of therapy depends on which of these

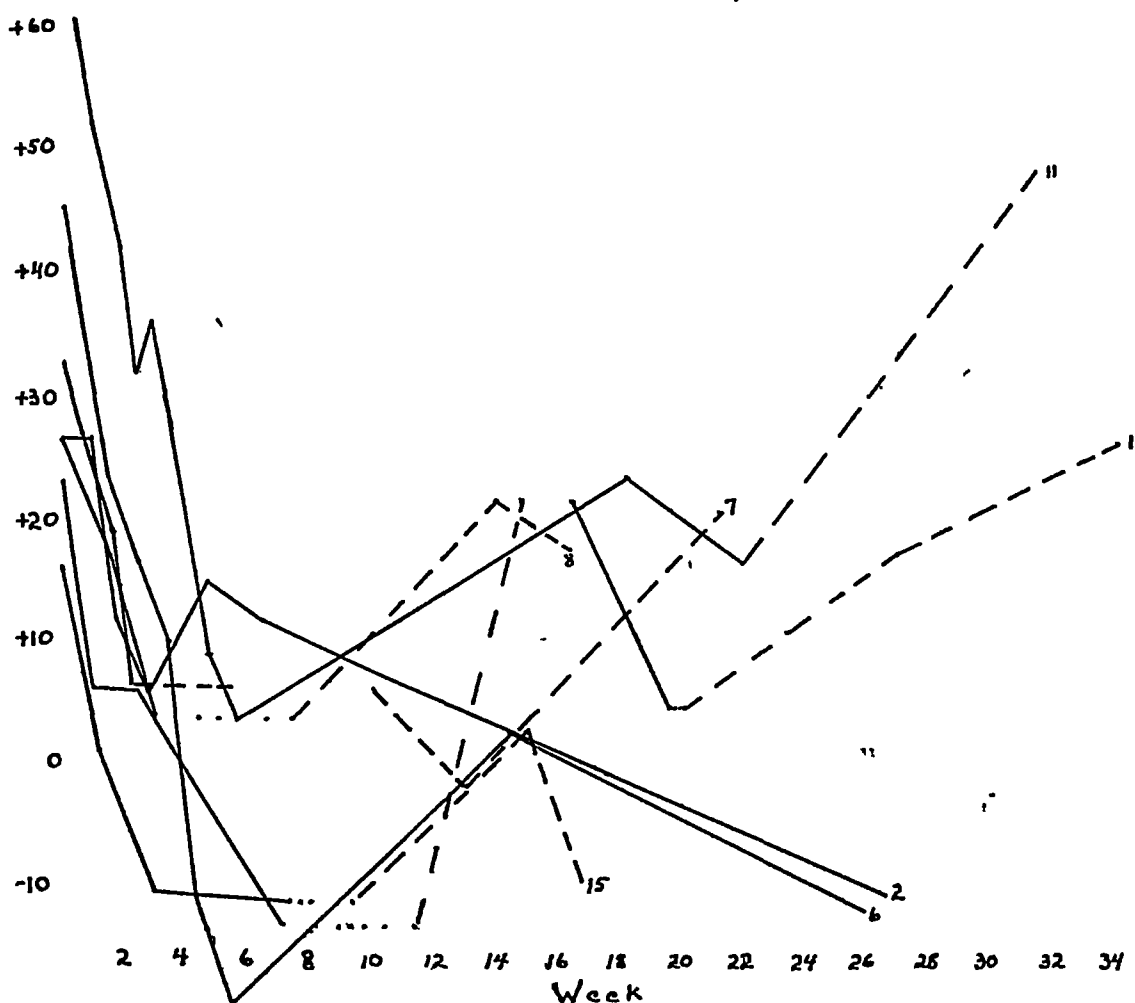


FIG 2 The effect of prolonged and intermittent thiouracil treatment on the BMR in seven cases. The numbers refer to the cases (see text). The interrupted lines indicate when the patient was not receiving the drug. The dotted lines indicate the time from the last BMR while the patient was receiving thiouracil until the time of cessation of thiouracil administration, no BMR being performed during this period.

ends one seeks. The latter would probably require far more therapy than the former. Unfortunately, however, we have no method of determining when a spontaneous remission would occur or whether thiouracil has induced such a remission. Finally, we have no idea as yet as to how long a period of therapy is necessary for exhaustion atrophy to set in.

That a state of "normality" can be obtained for prolonged periods is illustrated by many of our cases. In case 1, thiouracil was discontinued after two and one-half months of therapy. Nineteen days later the basal meta-

bolic rate had risen, she had lost weight and had noted a recurrence of her symptoms. On readministration of the drug, the basal metabolic rate promptly fell. The drug was stopped a second time. Six weeks later the basal metabolic rate had risen again, but her symptoms did not recur until 16 weeks after cessation of therapy.

In case 11, thiouracil therapy was stopped after 22 weeks. Nine weeks later, the basal metabolic rate had risen markedly. Many weeks later, however, she still continued asymptomatic.

In case 8, thiouracil was administered for eight weeks and then stopped. Six weeks later the basal metabolic rate had risen, but the symptoms had not recurred.

Case 10 received thiouracil for three and one-half months, and then it was stopped. Three months later, the basal metabolic rate had risen, but the symptoms did not return until five months had elapsed.

A very mild case of Graves' disease, case 15, received thiouracil for eight weeks. The drug was then stopped for a period of seven months. During this period of time she remained asymptomatic.

Astwood has reported nine cases with prolonged remission, the minimal period of treatment being six and one-half months. He has, however, noted recurrences after a treatment period of 151 days.

We shall now consider the other groups to see what effectiveness was exhibited by thiouracil therapy in spite of any untoward effects that may have occurred.

In the one instance of leukopenia, case 25, Lugol's solution had been administered for four months prior to entrance to the hospital. After two weeks of treatment with thiouracil, the basal metabolic rate had fallen slightly, the pulse had slowed, and she had gained weight. Because of a mild leukopenia, it was deemed advisable to discontinue the drug.

In the patients with drug fever, the period of study was too short to determine the response to therapy, inasmuch as fever occurred within 12 days.

The cases in group C, illustrating a lack of response, are four in number. Case 36 received thiouracil for 30 days during which time he gained weight and the pulse rate was reduced, but the basal metabolic rate remained elevated. Case 37 was treated for 19 days. The basal metabolic rate, pulse rate, and weight remained stationary. Case 38 received Lugol's solution prior to admission to the hospital. She was treated with thiouracil for 20 days with a resultant slight increase in the basal metabolic rate, slight weight loss, and no change in pulse rate. (This transitory rise in basal metabolic rate observed when thiouracil is administered directly after iodine has been employed has been noted by others.) These cases were treated early in our experience and we now feel that the period of therapy was too short. The last in group C case 39 was a 51 year old woman with recurrent hyperthyroidism. She had severe diabetes mellitus and auricular fibrillation. After four weeks of thiouracil therapy the basal metabolic rate fell from plus 40 to plus 16 per cent, and she gained weight. The diabetic status how

ever, did not improve. After a period of seven and one-half weeks of therapy she developed leukopenia with a white count as low as 1,400 with 48 per cent polymorphonuclear leukocytes. The drug was stopped for 11 days and then resumed with 0.2 gram instead of the previously employed 1 gram a day. This dosage was evidently not sufficient, and the basal metabolic rate rose to plus 52 per cent, and she again started to lose weight. The diabetes remained severe. The white count rose, but still remained low, and it was not deemed advisable to employ a larger dosage of thiouracil. After three months of therapy, her clinical progress remained unsatisfactory. She was then given Lugol's solution and operated upon.

The expected improvement of diabetes with correction of the hyperthyroidism has been reported by Astwood,<sup>19, 22</sup> and by Palmer,<sup>21</sup> but was not observed by McGavack et al.<sup>48</sup>

Group D includes three cases of hyperthyroidism successfully prepared for operation with the aid of thiouracil. Case 49 exhibited a marked response in the basal metabolic rate in two weeks, plus a gain in weight and a fall in pulse rate. She was operated upon successfully after 18 days of preparation. Case 42 showed a slow response. After four weeks the basal metabolic rate had fallen from plus 48 to plus 30 per cent, and the pulse remained rapid. He had, however, gained weight and felt subjectively improved. Operation was successfully performed.

CHART II

Blood Cholesterol Determinations before and after Thiouracil Therapy

| Before | Case | After |
|--------|------|-------|
| 180    | 5    | 360   |
| 180    | 6    | 360   |
| 260    | 2    | 310   |
| 150    | 3    | 230   |
| 200    | 14   | 400   |
| 170    | 16   | 160   |
| 290    | 21   | 300   |
| 180    | 23   | 340   |
| 140    | 4    | 280   |

Group E consists of three cases of non-toxic goiter. In cases 45 and 43 the administration of thiouracil for four and one-half and five weeks, respectively, was without effect on the basal metabolic rate, pulse rate, and weight. Also in a third case of non-toxic goiter with some features of a questionable mild hyperthyroidism, no effect was noted after four weeks of therapy.

*The Effect of Thiouracil on the Blood Cholesterol* The level of the blood cholesterol has never been a very good index of the degree of hyperthyroidism. Our data are still relatively incomplete. The data available show a rise in the blood cholesterol level in seven instances and no change in two, concomitant with clinical improvement (chart 2).

*The Effect of Therapy on Renal Function* In none of our cases have we noted any adverse effects on renal function as determined by routine urinary

examination and by the urine concentration test Palmer<sup>21</sup> noted one case of hematuria

*Effect of Thiouracil on Liver Function* Although Shorr<sup>21</sup> and Paschkis et al<sup>24</sup> each noted the onset of jaundice in one case, we have noted no impairment of liver function as the result of thiouracil therapy as measured by the presence of clinical jaundice, blood icterus index, cephalin flocculation test, urinary bile, and urobilinogen, and the galactose tolerance test

*Effect of Thiouracil on the Heart* We noted no evidence of cardiac damage as the result of thiouracil therapy Neither case with auricular fibrillation (cases 24 and 39) returned to normal rhythm Others have reported both a return to normal rhythm and a failure to return to normal rhythm

*Effects of Thiouracil on the Blood Constituents* No adverse effects were noted on the hemoglobin or red blood cell count The effects on the white count and sternal marrow will be detailed below

*Effect of Therapy on Exophthalmos* Exophthalmometric readings were performed on our patients, but we are not as yet ready to commit ourselves to any definite comment We have, however, seen no "malignant exophthalmos" follow thiouracil therapy, as did Williams and Bissell<sup>20</sup> It has been our impression that there occurs no recession in the exophthalmos

*Effect of Thiouracil on the Size of the Thyroid* It is difficult to measure accurately the size of the thyroid gland We have seen enlargement of the gland in several patients, especially those in the early stages of the illness, in whom the gland was large to begin with Recession in size, however, seemed to ensue later In other patients, we have noted no increase in size but rather a decrease of varying extent The glands appear to become somewhat softer, but this, too, is difficult to judge

*The Effect of Iodine on the Thiouracil Treated Patient* We have mentioned earlier that iodine used prior to thiouracil may result in a delay in the therapeutic result At times there actually occurs an early increase in the basal metabolic rate This lag is probably due to the storage of colloid by the thyroid gland while iodine is being administered A longer period is, therefore, required before the colloid can be utilized and the effect of thiouracil can be noted

We have had no experience in the simultaneous use of iodine and thiouracil Mackenzie and Mackenzie<sup>1b</sup> thought that iodides potentiated the effects of the sulfonamides Rawson et al<sup>25</sup> made comment on the glands of some patients treated with both, but no comment was made as to the clinical effect Astwood<sup>17</sup> found that iodine resulted in a further fall in the basal metabolic rate, and believed that it caused storage of thyroid hormone in the gland Williams<sup>20</sup> felt that no effect other than that of the thiouracil could be noted

In two instances in which iodine was used after thiouracil was discontinued, Williams<sup>20</sup> noted a slight increase in the basal metabolic rate Our experience in this regard is based on the use of iodine in preparation for opera-

tion in four cases of drug fever due to thiouracil, one case of leukopenia,<sup>25</sup> and case 39. In all instances iodine therapy was started after thiouracil had been discontinued.

Case 34 received 0.6 gram of thiouracil daily for 11 days, and then developed fever. Three days later he was given 0.2 gram and exhibited a recurrence of fever. Four days after this, he was given Lugol's solution, which he received for 12 days and was then operated upon. The basal metabolic rate before treatment was plus 44 per cent, after thiouracil plus 32 per cent, after iodine plus 25 per cent. With iodine therapy he gained seven pounds in weight and the pulse rate remained slow, as it had always been. He died two days postoperatively of a massive pneumonia, confirmed by postmortem examination. The postoperative clinical picture was not that of true storm, and at autopsy an extensive pneumonic consolidation of the right lower lobe was found.

Case 33 received thiouracil for 10 days, at which time he developed a rise in temperature to 103° F. Lugol's solution was started six days later and administered for 21 days. The basal metabolic rate before treatment was plus 41 per cent. It did not fall on thiouracil therapy, but fell after the administration of iodine without any intervening rise, to plus 22 per cent. He was operated upon successfully.

Case 35 received thiouracil for 10 days when there occurred an elevation in temperature. The drug was discontinued, but one dose of 0.2 gram was given three days later, directly followed by another episode of fever. Ten days later, Lugol's solution was administered and continued for 11 days. The basal metabolic rate before therapy was plus 23 per cent. It fell to plus 13 per cent after thiouracil. Further basal metabolism determinations were not performed but because of a gain in weight and a slowing of the pulse operation was performed and was not followed by any untoward results.

Case 32 had a basal metabolic rate of plus 47 per cent before therapy. She received thiouracil for eight days, and 0.2 gram one week later. The basal metabolic rate remained elevated. Ten days later she was given Lugol's solution. After seven days on iodine therapy the basal metabolic rate was minus 7 per cent.

Case 25 received iodine before entrance to the hospital. Thiouracil was given for 16 days and then after one day of delay Lugol's solution was administered for 10 days. The basal metabolic rate fell from plus 34 to plus 23 per cent on thiouracil. On iodine the basal metabolic rate fell to plus 20 per cent. The operation and postoperative course were uneventful.

Case 39 was on thiouracil for 65 days with only slight interruption. Lugol's solution was then administered over a period of one month. The basal metabolic rate fell from plus 52 per cent to plus 26, plus 18, plus 23, and finally to plus 19 per cent. The patient was successfully operated upon and made an uneventful recovery.

It is difficult to decide when the thiouracil effect wears off and when the iodine effect begins, and until there is accumulated a larger collection of data

with varying periods of thiouracil therapy and iodine administration, we shall not have the answers to our problems. But our data would seem to indicate that the use of iodine, following the cessation of thiouracil therapy, did not result in any untoward effects.

*The Toxic Effects of Thiouracil Therapy* The toxic effects that we have encountered are tabulated in chart 3.

### CHART III

#### Toxic Manifestations of Thiouracil

- A Indications for further therapy
  - 1 Conjunctivitis—5 cases
  - 2 Edema—1 case
  - 3 Variegated complaints
    - Dizziness
    - Aches and pains
    - Burning in throat
- B Contraindications for further therapy
  - 1 Drug fever with rash—2 cases
  - 2 Drug fever without rash—2 cases
  - 3 Agranulocytosis—6 cases
  - 4 Leukopenia—3 cases

*Conjunctivitis* There were five cases of conjunctivitis. One occurred during the first week of therapy, and three occurred during the second and third weeks. All were mild and transient, in spite of the fact that the drug was continued. One occurred after two and one-half months of treatment, was rather intense and persisted for several weeks, but disappeared during further treatment with thiouracil.

*Edema* One case of frank diffuse edema occurred after five weeks of treatment. No cause other than the thiouracil therapy could be established as the underlying factor. The urine and kidney function tests were negative. The total proteins of the blood were 6.0 grams per cent. The albumin fraction was 4.5, and the globulin fraction was 1.5 grams per cent. The serum sodium was 138.6 milliequivalents per liter, and chlorides 108.0. The basal metabolic rate was plus 1 per cent. The edema receded spontaneously and did not recur with further therapy. Other instances of edema have been reported by Williams et al.<sup>18</sup> who studied these cases intensively, and by Palmer.<sup>21</sup>

Slight transient puffiness of the eyes was complained of by several other patients.

*Variegated Complaints* There were rather frequent complaints of dizziness and aches and pains in the joints that had not been present before treatment with thiouracil was begun. Whether these were simply psychoneurotic in origin or related to the drug administration we cannot say. Others complained of burning in the throat after ingestion of the drug. In a few transient skin eruptions were noted that disappeared in spite of the continuation of treatment. Other observers have noted similar rashes.

*Drug Fever* There were four instances of drug fever, including two previously reported by Gabrilove and Kert.<sup>22</sup> Two of these were accom-



panied by a generalized maculopapular rash, and one of these latter had a generalized lymphadenopathy. In three of these patients a single subsequent dose of 0.2 gram of thiouracil provoked a recurrence of the fever and thereby proved the drug origin of the pyrexia. The fever began on the eighth, tenth, tenth, and eleventh day after thiouracil therapy was instituted.

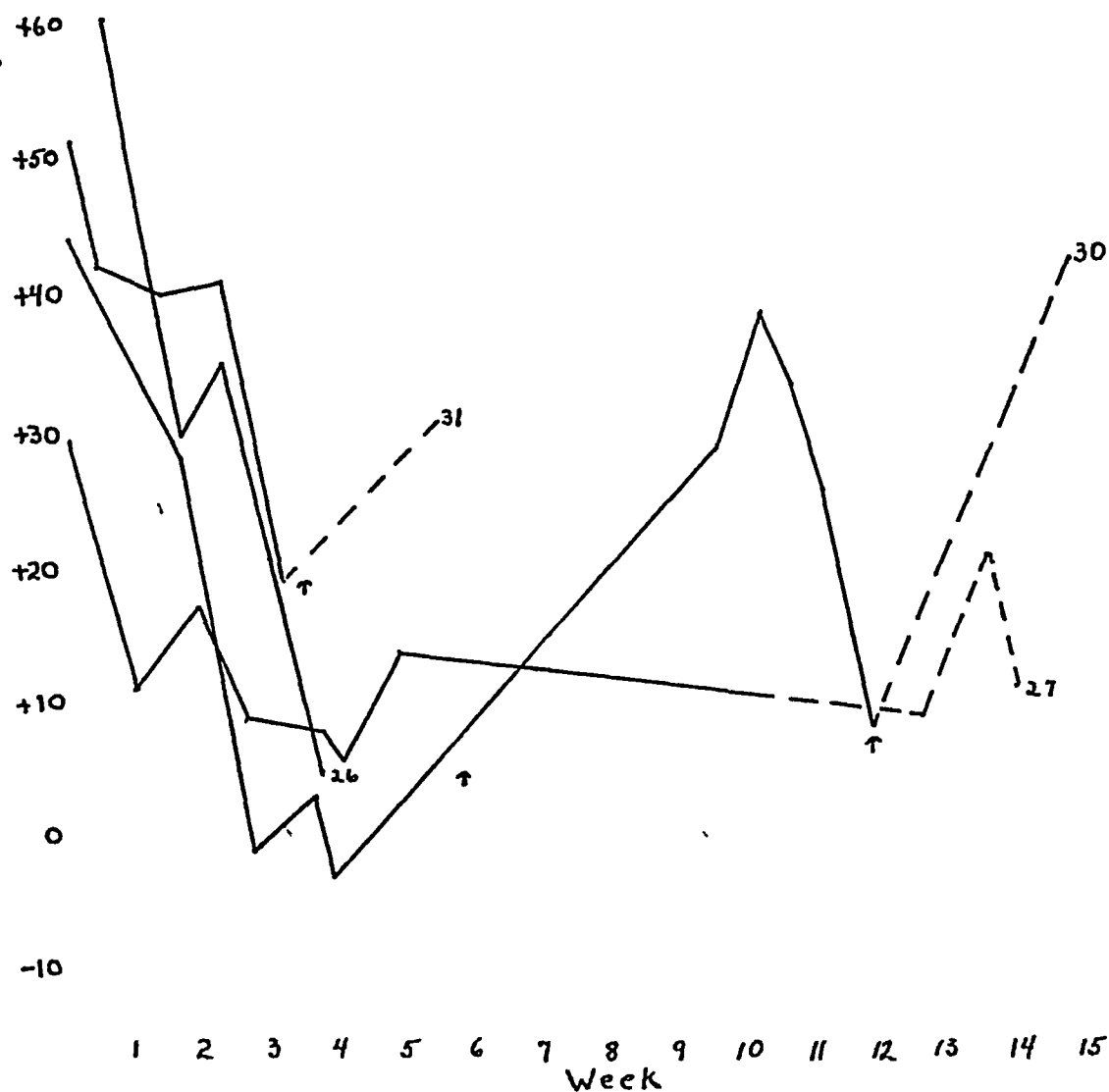


FIG 3 The effect of thiouracil on the BMR in four cases developing agranulocytosis. The arrows indicate the onset of agranulocytosis. The interrupted lines indicate the time during which the patient was not receiving the drug.

*Agranulocytosis.* The most dangerous, and unfortunately comparatively frequent, complication of thiouracil therapy is agranulocytosis (granulocytopenia). We have encountered six cases of agranulocytosis in cases of hyperthyroidism treated with thiouracil.

The first case in our experience was that of a 47 year old woman with hyperthyroidism, who had an excellent response to thiouracil (case 26, figure 3). She was discharged from the hospital markedly improved. At the end of four and one-half weeks of therapy of 1 gram a day her white blood

count was 5,800, with a normal differential. She was discharged from the hospital for follow-up study in the clinic. She was readmitted 12 days later. Three days prior to her readmission, she noted fever, chills, a congested nose and throat, cough and dysphagia. The thiouracil which she had been taking in daily doses of 0.4 gram was discontinued. A blood smear taken at this time, but examined only at the time of readmission, revealed six segmented polymorphonuclear leukocytes, two non-segmented polymorphonuclear leukocytes, 90 lymphocytes and two monocytes. On admission, the hemoglobin

## CHART IV

(Case 29)

Detailed Blood and Sternal Marrow Studies on a Patient Who Developed Agranulocytosis with Thiouracil Therapy

| Day of Admission     | -21   | -1    | 0     | 1     | 2     | 3     | 5     | 6     | 7     | 11      | 14      | 20    |
|----------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------|---------|-------|
| Hemoglobin           | 100   | 86    | 80    | 85    | 72    | 80    |       | 105   | 117   | 111     | 101     |       |
| R B C                | 4.76  | 4.62  |       | 4.65  |       |       |       |       |       | 5.54    |         |       |
| Platelets            |       |       |       | 300   |       |       |       | 210   |       |         |         |       |
| W B C                | 7,500 | 3,250 | 2,240 | 1,250 | 1,400 | 1,700 | 4,100 | 5,100 | 7,250 | 114,000 | 138,000 | 7,650 |
| Myelocytes           |       |       |       |       |       |       |       | 5     |       |         |         |       |
| Non-Seg. Neutrophils | 10    | 2     |       | 3     | 2     |       | 7     | 9     | 6     | 6       | 10      |       |
| Seg. Neutrophils     | 55    | 1     |       |       |       | 1     | 4     | 28    | 50    | 52      | 61      | 69    |
| Lymphocytes          | 33    | 97    | 98    | 95    | 98    | 96    | 84    | 48    | 35    | 38      | 18      | 26    |
| Monocytes            | 2     |       | 2     |       |       | 3     | 2     | 9     | 9     | 4       | 6       | 5     |
| Basophile            |       |       |       | 1     |       |       |       |       |       |         | 1       | 1     |
| Eosinophile          |       |       |       |       |       |       |       | 1     |       |         | 1       |       |
| Plasma               |       |       |       | 1     |       |       |       |       |       |         |         |       |

## Sternal Marrow Puncture

|                      |  |  | 15,000 | 120,000 |  |  | 110,000 |  |  |  |
|----------------------|--|--|--------|---------|--|--|---------|--|--|--|
| Nucleated Count      |  |  | 0      | 11      |  |  | 44      |  |  |  |
| Megakaryocyte        |  |  | 50     | 20      |  |  | 20      |  |  |  |
| Myeloblast           |  |  | 90     | 110     |  |  | 452     |  |  |  |
| N Myelocyte          |  |  | 0      | 0.5     |  |  | 0.4     |  |  |  |
| E Myelocyte          |  |  | 0      | 0.5     |  |  | 0       |  |  |  |
| B Myelocyte          |  |  | 20     | 0       |  |  | 172     |  |  |  |
| Non Seg. Neutrophils |  |  | 0      | 0       |  |  | 24      |  |  |  |
| Seg. Neutrophils     |  |  | 320    | 135     |  |  | 72      |  |  |  |
| Lymphocyte           |  |  | 160    | 120     |  |  | 75      |  |  |  |
| Hematogone           |  |  | 30     | 4.5     |  |  | 0.6     |  |  |  |
| Plasma Cell          |  |  | 70     | 30      |  |  | 0       |  |  |  |
| Reticulum Cell       |  |  | 10     | 0       |  |  | 0       |  |  |  |
| Monocyte             |  |  | 10     | 0.5     |  |  | 0       |  |  |  |
| Megakaryoblast       |  |  | 20     | 20      |  |  | 0.8     |  |  |  |
| Erythroblast         |  |  | 210    | 435     |  |  | 180     |  |  |  |
| Normoblast           |  |  |        |         |  |  |         |  |  |  |

was 87 per cent, the red blood count 4.53 million, white count 200 with 100 per cent lymphocytes. The platelets were 120,000. Sternal marrow aspiration revealed 11,000 nucleated cells with a differential of 8 per cent myeloblasts, 20 per cent lymphocytes, 10 per cent hematogones, 10 per cent plasma cells, 20 per cent reticulum cells, 30 per cent normoblasts, and 2 per cent megakaryocytes. In spite of treatment with intravenous sulfamerazine and blood transfusions, she died on the third hospital day. Just prior to her death, the white count was 800 cells per cu mm with 100 per cent lymphocytes. The blood culture was sterile.

The remaining five cases in our series all survived. We attribute these good results to the generous use of penicillin and blood transfusions. This therapy served to control infection and enabled the patients to survive until such time as granulocyte formation was again normally resumed.

The second case in our series was a 50 year old woman treated by her private physician for hyperthyroidism with thiouracil. She had responded well to 0.5 gram a day for seven weeks. One day prior to admission she noted fever, sore throat and headache. A white blood cell count was 3,250 per cu mm, of which 97 per cent were lymphocytes and one was a polymorphonuclear leukocyte. The next day the total white count had fallen to 2,240, and the day after to 1,250 per cu mm with a total absence of granulocytes. Chart 4 summarizes the blood findings in this case. She was treated with penicillin and blood transfusions. Her temperature remained elevated for five days and then began to return to normal levels. Concomitantly there occurred a progressive improvement in the peripheral blood and bone marrow.

CHART V

(Case 27)

## Blood and Sternal Marrow Studies in a Patient with Agranulocytosis

| Day of Admission    | -9    | 0     | 1    | 2   | 3     | 4     | 5  | 6     | 7     | 11     | 16    |
|---------------------|-------|-------|------|-----|-------|-------|----|-------|-------|--------|-------|
| Hemoglobin          | 75    |       | 76   | 86  |       | 86    |    |       |       | 105    |       |
| Red Count           | 4.2   |       | 4.19 |     |       | 4.75  |    |       |       | 5.45   |       |
| Platelets           |       |       |      | 300 |       | 310   |    |       |       |        |       |
| White Count         | 5,100 | 1,200 | 600  | 950 | 2,350 | 2,400 |    | 5,400 | 5,850 | 11,300 | 7,650 |
| Myelocytes          | 8     |       |      | 2   |       |       | 6  | 1     | 3     | 2      |       |
| Non-Seg Neutrophils |       | 6     | 8    | 10  | 18    | 12    | 23 | 27    | 15    | 14     | 6     |
| Seg Neutrophils     | 60    | 2     | 6    | 2   | 29    | 14    | 10 | 28    | 37    | 41     | 54    |
| Lymphocyte          | 34    | 90    | 84   | 48  | 36    | 62    | 50 | 37    | 38    | 34     | 32    |
| Monocyte            | 5     | 2     | 2    | 28  | 10    | 6     | 8  | 4     | 2     | 5      | 7     |
| Basophile           |       |       |      | 2   | 1     |       |    |       |       | 2      | 1     |
| Eosinophile         | 1     |       |      | 2   | 1     | 2     | 2  | 2     |       | 2      |       |
| Plasma              |       |       |      |     | 3     |       | 1  | 1     | 5     | 2      |       |

## Sternal Marrow Studies

|                     |  |      |      |  |  |  |  |  |  |      |
|---------------------|--|------|------|--|--|--|--|--|--|------|
| Nucleated Count     |  | 70   | 105  |  |  |  |  |  |  | 475  |
| Megakaryocyte       |  | 88   | 132  |  |  |  |  |  |  | 110  |
| Myeloblasts         |  | 4.0  | 3.6  |  |  |  |  |  |  | 0.2  |
| N Myelocytes        |  | 34.0 | 61.6 |  |  |  |  |  |  | 32.1 |
| E Myelocytes        |  | 2.0  | 0    |  |  |  |  |  |  | 0.3  |
| Non-Seg Neutrophils |  | 0    | 0    |  |  |  |  |  |  | 10.0 |
| Seg Neutrophils     |  | 0    | 0    |  |  |  |  |  |  | 6.6  |
| Eosinophils         |  | 2.8  | 0.4  |  |  |  |  |  |  | 0.6  |
| Lymphocytes         |  | 20.4 | 7.6  |  |  |  |  |  |  | 1.1  |
| Hematogone          |  | 7.6  | 9.2  |  |  |  |  |  |  | 3.3  |
| Reticulum           |  | 1.2  | 0.8  |  |  |  |  |  |  | 0.3  |
| Plasma              |  | 1.6  | 1.2  |  |  |  |  |  |  | 0    |
| Megakaryocyte       |  | 0.4  | 0.4  |  |  |  |  |  |  | 0    |
| Megaloblast         |  | 0    | 0    |  |  |  |  |  |  | 0.3  |
| Erythroblast        |  | 0    | 0.4  |  |  |  |  |  |  | 0.7  |
| Normoblast          |  | 25.6 | 11.8 |  |  |  |  |  |  | 8.3  |

The third case, case 27, was that of a 43 year old woman with hyperthyroidism. She was treated with thiouracil with dosages of one gram a day for 32 days and then 0.2 gram for 34 days. She had been hospitalized for the first 37 days of the therapy, and then was seen in the clinic weekly. Nine days prior to admission she had had a blood count, which was entirely normal. Five days prior to admission, she developed fever, cough, sore throat, a "stuffed" nose, and headache, and she stopped taking thiouracil. She was sent into the hospital, where the white blood cell count was found to be 1,200 per cu mm, of which only 8 per cent were of the granulocytic series. The next day, the count had fallen to 600, although 14 per cent were

now polymorphonuclear leukocytes. She was treated with penicillin, blood transfusions, and liver extracts, and responded very well. The febrile course lasted four days. Her hematological picture is illustrated in chart 5.

The fourth case was that of a 58 year old man with hyperthyroidism, who was treated with 0.6 gram of thiouracil for 22 days, and then 0.2 gram for 44 days. While under observation in the hospital, he developed agranulocytosis. The white blood cell count fell to 1,600 per cu mm, of which 2 per cent belonged to the granulocytic series. The changes in his marrow and peripheral blood are illustrated in charts 6 and 7. He was treated with penicillin, pentnucleotide, and blood transfusions. He was febrile for six days, but did well thereafter (case 30).

CHART VI

(Case 30)

## Peripheral Blood Studies in a Patient with Agranulocytosis

| Date | Hemo-<br>globin | R B C | W B C | Seg Neut | Non Seg<br>Neut | Lympho-<br>cyte | Monocyte | Eosinophile |
|------|-----------------|-------|-------|----------|-----------------|-----------------|----------|-------------|
| 4/15 |                 |       | 8,500 | 61       | 4               | 24              | 8        | 3           |
| 6/20 | 82              | 4.38  | 6,300 | 45       | 2               | 44              | 3        | 3           |
| 6/23 |                 |       | 4,000 | 54       | 5               | 36              | 2        | 3           |
| 6/27 |                 |       | 3,700 | 53       | 2               | 44              | 1        |             |
| 7/3  |                 |       | 2,200 | 21       | 5               | 72              |          | 2           |
| 7/6  |                 |       | 1,900 | 3        | 4               | 92              |          | 1           |
| 7/7  |                 |       | 1,600 | 2        | 1               | 97              |          |             |
| 7/8  | 72              |       | 1,900 | 1        |                 | 99              |          |             |
| 7/10 |                 |       | 1,900 | 1        |                 | 99              |          |             |
| 7/11 |                 |       | 1,600 | 1        |                 | 97              | 1        | 1           |
| 7/12 | 68              |       | 1,900 | 1        |                 | 99              |          |             |
| 7/13 |                 |       | 2,000 | 1        |                 | 99              |          |             |
| 7/14 |                 |       | 1,900 | 2        | 2               | 96              |          |             |
| 7/15 |                 |       | 2,100 | 2        |                 | 94              | 4        |             |
| 7/17 |                 |       | 3,000 | 20       | 6               | 72              | 2        |             |
| 7/18 |                 |       | 3,500 | 14       | 5               | 78              | 3        |             |
| 7/20 |                 |       | 4,200 | 3        | 10              | 60              |          |             |
| 7/22 |                 |       | 4,000 |          |                 |                 |          |             |
| 7/25 | 90              |       | 7,000 | 33       | 2               | 60              | 15       |             |

CHART VII

(Case 30)

## Sternal Marrow Studies

|                       | 7/5    | 7/13   |
|-----------------------|--------|--------|
| Nucleated Count       | 96,000 | 80,000 |
| Megakaryocyte         | 22     | 44     |
| Mycloblasts           | 2.0    | 5.2    |
| Promyelocytes         | 0.4    | 0      |
| N Myelocyte           | 0      | 36.0   |
| E Myelocyte           | 0.8    | 1.2    |
| Non-Seg. Neutrophiles | 0.8    | 0.5    |
| Eosinophile           | 0.4    | 0.4    |
| Lymphocyte            | 3.0    | 7.2    |
| Hematogone            | 58.8   | 7.6    |
| Plasma                | 0      | 0.8    |
| Reticulum             | 0      | 0.4    |
| Megakaryocyte         | 0      | 0.1    |
| Erythroblast          | 5.6    | 1.6    |
| Normoblast            | 28.8   | 38.1   |

The fifth case, that of a 53 year old man with hyperthyroidism (case 31), also afforded us the opportunity to study the development of agranulocytosis while the patient was hospitalized. He was treated with 0.6 gram a day for 25 days when he developed sore throat and fever. A white blood cell count at this time showed the presence of only 950 cells per cu mm, of which 10 per cent belonged to the granulocytic series. The next day, although the total white count had increased to 1,575 per cu mm, the granulocytes had entirely disappeared from the peripheral blood. The changes in the peripheral blood and sternal marrow are illustrated in charts 8 and 9. He was treated with penicillin and blood transfusions, was febrile for 10 days, and then recovered completely.

The sixth case (case 28), the details of which were furnished by Dr N Rosenthal, who treated this patient in the Private Pavilion of The Mount Sinai Hospital, was a 29 year old woman with hyperthyroidism, who had received 0.6 gram of thiouracil a day for 35 days. Blood counts were not done. Five days prior to entrance into the hospital, she noted fever and painful gums. She was seen by her physician and by her dentist, and was then referred to Dr Rosenthal. On the third day of this patient's hospital admission, the total white blood cell count had fallen to 600 per cu mm, with only one basophile in the peripheral blood, representing the granulocytic series. She was treated with liver extract, penicillin, and blood transfusions, and did well, being febrile for only five days. Her hematological picture is illustrated in charts 10 and 11.

The time of occurrence of the agranulocytosis in these cases was 40, 49, 66, 80, 25, and 35 days after onset of therapy. The total dosages employed were 15.0, 21.0, 24.5, 27.6, 34.6, and 49.0 grams.

We do not believe that these toxic reactions are due to a direct depression of the marrow by an overdosage of drug, but rather that it represents a curious sensitivity on the part of the patient, similar to that observed with other drugs with a similar organic nucleus.

These hematological complications will be reported in greater detail by Drs Vogel, Tyson, and Rosenthal.

We wish to call attention to our results in the treatment of agranulocytosis with penicillin and blood transfusions. Of the six patients with this unfortunate complication, one died and the remaining five recovered. This fatality occurred prior to our use of chemotherapy in these cases. In the remaining five patients, penicillin was administered in a dosage of 20,000 units intramuscularly every three hours day and night, and small blood transfusions were given daily. Since the primary cause of death in the patients with agranulocytosis is overwhelming infection, the rationale for the use of penicillin is postulated on the attempt to control such infection until such time as the normal formation of granulocytes is resumed.

*Anatomical Changes in the Thyroid Gland Following the Use of Thiouracil*. From animal experimentation with thiouracil detailed previously

## CHART VIII

(Case 31)

## Peripheral Blood Studies in a Patient with Agranulocytosis

| Date | Hemo-<br>globin | R B C | Platelet<br>(thousand) | W B C | Segmented<br>Polymor-<br>phonuclear<br>Leukocyte | Non-Seg-<br>mented<br>Polymor-<br>phonuclear<br>Leuko-<br>cyte | Lymph-<br>ocyte | Mono-<br>cyte | Eosino-<br>phile | Plasma | Micro-<br>phage |
|------|-----------------|-------|------------------------|-------|--|--|-----------------|---------------|------------------|--------|-----------------|
| 7/13 | 83              | 4 52  |                        | 8,550 | 57   | 6  | 33              | 4             |                  |        |                 |
| 7/24 | 75              |       |                        | 5,450 | 45   | 2  | 47              | 3             | 3                |        |                 |
| 7/26 | 79              |       |                        | 6,000 | 43   | 5  | 40              | 6             | 6                |        |                 |
| 7/28 | 78              |       |                        | 3,600 | 40   | 7  | 45              | 1             | 3                |        |                 |
| 7/31 | 81              |       |                        | 4,800 | 48   | 7  | 35              | 8             | 2                |        |                 |
| 8/4  | 80              |       |                        | 3,700 | 37   | 3  | 57              | 1             | 2                |        |                 |
| 8/7  | 70              |       |                        | 3,550 | 43   | 8  | 47              | 1             | 1                |        |                 |
| 8/9  | 79              |       |                        | 4,800 | 40   | 10   | 47              | 4             |                  | 2      |                 |
| 8/11 | 68              |       |                        | 950   | 6  | 3  | 88              | 2             | 1                |        |                 |
| 8/12 | 69              | 4 1   | 300                    | 1,575 |  |  | 98              | 2             |                  |        |                 |
| 8/13 |                 |       |                        | 1,000 |  |  | 80              | 20            |                  |        |                 |
| 8/14 | 85              |       |                        | 1,450 |  |  | 98              | 2             |                  |        |                 |
| 8/15 | 80              | 4 4   | 260                    | 1,400 |  |  | 99              | 1             |                  |        |                 |
| 8/16 | 79              | 4 5   |                        | 1,200 |  |  | 99              | 1             |                  |        |                 |
| 8/17 |                 |       |                        | 1,200 |  |  | 99              | 1             |                  |        |                 |
| 8/18 | 75              |       |                        | 1,300 |  |  | 96              | 2             |                  | 2      |                 |
| 8/19 |                 |       |                        | 1,750 |  | 2  | 94              | 4             |                  |        |                 |
| 8/20 |                 |       |                        | 2,200 | 3  | 1  | 85              | 7             | 4 myelocytes     |        |                 |
| 8/21 |                 |       |                        | 2,650 | 5  | 13   | 77              | 5             |                  |        |                 |
| 8/22 |                 | 5 5   | 260                    | 3,100 | 9  | 18   | 62              | 11            |                  |        |                 |
| 8/23 |                 |       |                        | 3,450 | 13   | 14   | 68              | 5             |                  |        |                 |
| 8/24 | 107             |       |                        | 2,750 | 13   | 10   | 66              | 10            |                  |        |                 |
| 8/25 | 102             |       |                        | 4,500 | 22   | 11   | 53              | 13            |                  |        | 1               |
| 8/26 |                 |       |                        | 4,050 | 55   | 8  | 28              | 9             |                  |        |                 |

## CHART IX

(Case 31)

## Sternal Marrow

| Date                       | 8/11   | 8/16   | 8 22    |
|----------------------------|--------|--------|---------|
| Nucleated Count            | 50,000 | 45,000 | 175,000 |
| Megakaryocytes             | 66     | 44     | 44      |
| Myeloblasts                | 2 0    |        | 2 0     |
| Promyelocytes              |        | 0 5    | 12 7    |
| Myelocytes, Neutrophile    |        |        | 55 0    |
| Myelocytes, Eosinophiles   |        |        | 0 7     |
| Non-Segmented Neutrophiles |        |        | 10 0    |
| Segmented Neutrophiles     | 0 4    |        | 1 0     |
| Lymphocyte                 | 17 6   | 3 5    | 2 0     |
| Hematogone                 | 6 8    | 7 0    | 2 3     |
| Plasma                     | 2 0    | 5 5    | 3 0     |
| Reticulum                  | 0 8    | 2 0    | 1 0     |
| Myeloblast                 | 0 4    | 0 5    |         |
| Erythroblast               | 0 8    | 4 5    | 0 3     |
| Monoblast                  | 69 2   | 76 0   | 10 0    |
| Megakaryocyte              |        | 0 5    |         |

we have learned what the anatomical changes are that occur in the thyroid glands. These changes are diffuse hyperplasia and hypertrophy of the gland, lymphoid infiltration, and increased vascularity. However, changes in the human being treated with thiouracil may not occur to the same degree as in animals, for several reasons. Evaluation of treatment in a patient with hyperthyroidism is often very difficult, for one must take into account the length of time the disease has existed, the previous use of iodine and radiotherapy, the natural history of remission and relapse, and the varying degrees of severity. The thyroid gland may reflect in its histology all of these factors, so that even the gland from an untreated patient may show various types of change, varying from marked hyperplasia to marked involution. The knowledge that the human thyroid may go through a cycle of hyperplasia and involution (Marine cycle) must be borne in mind. The thyroid glands of experimental animals are "biologically young" and easily susceptible to external influence, but in man, the thyroid gland, having passed through varying numbers of cycles, depending on the stage of the disease, may be resistant to induced change. There may be several adenomata and foci of nonresponsive thyroid tissue present. Patients in the early stages of thyrotoxicosis with diffuse hyperplasia are probably the patients whose thyroid glands are most satisfactory for study. There are many other factors which influence the appearance of the gland after thiouracil treatment. For example, patients with hyperthyroidism have hyperplasia and hypertrophy as part of the picture of the underlying disease. It is, therefore, difficult to decide how much is due to the disease and how much is due to the drug, unless a biopsy had been taken before the administration of the drug.

The period of treatment with thiouracil is relatively short, and the dosage is relatively small compared to the dosage employed in animal experimentation. The changes, therefore, may not be so striking in the human gland.

Finally, patients with normal thyroids or colloid goiter may have a large store of colloid and thyroid hormone. It will, therefore, take a considerable time to deplete these stores and consequently a longer period of time for the clinical effects of the drug to be noted and the anatomical effects to occur. We presume that the hyperplasia results from the low levels of circulating thyroid hormone with a resultant stimulation of thyrotropic hormone secretion and not as the result of the prevention of manufacture of thyroid hormone *per se*.

Other factors, such as the use of iodine before, during, or after thiouracil, alter the histological picture and make any interpretation difficult. Only by collecting a large number of cases, changing one variable at a time, will we be able to weave the entire picture.

The glands that we have available for study are (A) one case in which death resulted from agranulocytosis (case 26) and three cases of hyperthyroidism prepared for operation with thiouracil (cases 40, 41, 42), all of these cases representing the action of thiouracil in hyperthyroidism, (B) three cases of non-toxic goiter treated with thiouracil preoperatively to note

the effect of the drug, (C) eight cases of hyperthyroidism prepared with thiouracil for varying periods of time and followed by the use of iodine for a minimum of two weeks

In case 26, there were seen the most characteristic hypertrophy and hyperplasia. The thyroid gland was diffusely enlarged. The history of hyperthyroidism had been of two years' duration, thiouracil had been employed for about six weeks.

In case 40, the gland clinically was diffusely enlarged. The symptoms were of eight months' duration, and thiouracil had been employed for 18 days. In this gland, too, there was considerable hypertrophy and hyperplasia. A few small acini were seen filled with colloid.

In case 41, the histological picture was that of a micro- and macro-follicular adenoma.

In the group of non-toxic goiter, there was one gland which exhibited marked hyperplasia and tremendous amounts of lymphoid tissue. Whether the latter bears any relation to the thiouracil therapy or whether it was present before treatment, we cannot say. Such collection of lymphoid tissue has been reported by others.

The other two glands revealed colloid adenomata, one with a papillomatous area, the other with the trabecular adenoma.

Of the other cases studied, which have received thiouracil followed by iodine (cases 30, 34, 33, 35, 25, 38, 39, 37), one case (34) showed tremendous hyperplasia and hypertrophy. Six showed a histological appearance similar to that seen in Graves' disease in a colloid phase, two being rather hyperplastic. One showed the structure of a micro- and macro-follicular adenoma, but the gland clinically was rather nodular (case 35).

### SUMMARY

1 Thiouracil has been used in the treatment of 54 patients. Fifty-one patients of this group had hyperthyroidism, and three were instances of non-toxic goiter.

2 Thirty-three of these patients have been treated successfully with thiouracil for varying periods of time, the longest period of continuous therapy being 10 months. Four of these patients had recurrent hyperthyroidism, the remainder of the patients had diffuse hyperplasia or toxic nodular goiter.

3 Three patients with hyperthyroidism were successfully prepared for operation with thiouracil.

4 Four patients with hyperthyroidism failed to respond satisfactorily to thiouracil. These patients were subsequently prepared with iodine and successfully operated upon.

5 In 11 instances, thiouracil therapy was discontinued because of severe toxic reactions.



6 The following toxic reactions were encountered conjunctivitis, five cases (9 per cent), edema, one case (2 per cent), drug fever, four cases (7 per cent), leukopenia, one case (2 per cent), agranulocytosis, six cases (11 per cent). Some sort of toxic reaction was encountered in 31 per cent. One of the patients with agranulocytosis died (2 per cent).

7 The development of agranulocytosis or drug fever are indications for cessation of therapy. Treatment may be safely continued in the presence of conjunctivitis.

8 Liver and kidney function studies throughout the course of treatment failed to demonstrate any evidence of injury to these organs resulting from the thiouracil. However, instances of toxic hepatitis occurring during thiouracil therapy have been reported.

9 Because of the frequency and severity of the toxic reactions it is our feeling that thiouracil should be used under the following circumstances:

(a) In the preparation of iodine-fast patients for operation

(b) In older individuals with hyperthyroidism, in whom for one reason or another operation is fraught with great hazard

(c) In patients with recurrent hyperthyroidism who have been operated upon twice or more

#### BIBLIOGRAPHY

- 1 (a) CHESNEY, A M, CLAWSON, T A, and WEBSTER, B Incidence and characteristics of endemic goiter in rabbits, *Bull Johns Hopkins Hosp*, 1928, xliii, 261
- (b) WEBSTER, B, CLAWSON, T A, and CHESNEY, A M Heat production in goitrous and non-goitrous animals, *Bull Johns Hopkins Hosp*, 1928, xliii, 278
- (c) WEBSTER, B, and CHESNEY, A M Effect of administration of iodine on endemic goiter in rabbits, *Bull Johns Hopkins Hosp*, 1928, xliii, 291
- 2 WEBSTER, B, and CHESNEY, A M Studies in the etiology of simple goiter, *Am Jr Path*, 1930, vi, 275
- 3 MARINE, DAVID, and BAUMANN, E J Further studies on the etiology of goiter the effect of cyanides, *Trans Assoc Am Phys*, 1932, xlvii, 261
- 4 MARINE, DAVID The pathogenesis and prevention of simple or endemic goiter, *Jr Am Med Assoc*, 1935, civ, 2334
- 5 SHARPLESS, G P, PFARSON, J, and PRATO, G S Production of goiter in rats with raw and treated soy bean flour, *Jr Nutr*, 1939, xvii, 545
- 6 SHARPLESS, G R A new goiter-production diet for the rat, *Proc Soc Exper Biol and Med*, 1938, xxxviii, 166
- 7 WILGUS, H S, GASSNER, F X, PATTON, A R, and GUSTAVSON, R G The goitrogenicity of soy beans, *Jr Nutr*, 1941, xxii, 43
- 8 BARKER, M H, LINDBERG, H A, and WOOD, M H Further experiences with thiocyanates, *Jr Am Med Assoc*, 1941, cxvii, 1591
- 9 RAWSON, R W, HEPTER, S, and MANS, J H Cyanate goiter in man Report of a case with histological and metabolic studies, *Jr Clin Invest*, 1942, xxi, 624
- 10 RICHTER, C P, and CLEGG, K H Graying of hair produced by ingestion of phenylthiocarbamide, *Proc Soc Exper Biol and Med*, 1941, xlvii, 684
- 11 RICHTER, C P, and CLEGG, K H Toxic effects of the bitter tasting phenylthiocarbamide, *Arch Path*, 1942, xxxiii, 46
- 12 (a) KENNEDY, T H, and PETERS, H D The effect of Brassica seed diets on rats, *Brit Jr Exper Path*, 1941, xxii, 211

- (b) GRIESBACH, W E Changes in the anterior pituitary of the rat produced by Brassica seed diet, *Brit Jr Exper Path*, 1941, xii, 245
- (c) GRIESBACH, W E, KENNEDY, T H, and PURVES, H D The effect of goitrogenic diet on hypophysectomized rats, *Brit Jr Exper Path*, 1941, xii, 249
- 13 MACKENZIE, J B, MACKENZIE, C G, and MCCOLLUM, E V The effect of sulfanylguanidine on the thyroid of the rat, *Science*, 1941, xciv, 518
- 14 MACKENZIE, J B, and MACKENZIE, C G The effect of the "sulfa" drugs on the thyroid gland in rats and mice, *Federation Proc*, 1942, i, 122
- 15 KENNEDY, T H Thioureas as goitrogenic substances, *Nature*, 1942, cl, 233
- 16 MACKENZIE, C G, and MACKENZIE, J B Effect of sulfonamides and thiourea on the thyroid gland and basal metabolism, *Endocrinology*, 1943, xxxii, 185
- 17 ASTWOOD, E B, SULLIVAN, J, BISSELL, A, and TISLOWITZ, R. Action of certain sulfonamides and thiourea upon the function of the thyroid gland of the rat, *Endocrinology*, 1943, xxxii, 210
- 18 ASTWOOD, E B The chemical nature of compounds which inhibit the function of the thyroid gland, *Jr Pharmacol and Exper Therap*, 1943, lxxviii, 79
- 19 ASTWOOD, E B Treatment of hyperthyroidism with thiourea and thiouracil, *Jr Am Med Assoc*, 1943, cxlii, 78
- 20 WILLIAMS, R J, and BISSELL, G W Thiouracil in the treatment of thyrotoxicosis, *New England Jr Med*, 1943, ccxxix, 97
- 21 PALMER, V Hyperthyroidism and thiouracil, *Bull School Med, Univ Maryland*, 1944, xxviii, 125
- 22 ASTWOOD, E B Medical treatment of hyperthyroidism, *Bull New England Med Centre*, 1944, vi, 1
- 23 BARTELS, E C Thiouracil (its use in the preoperative management of severe hyperthyroidism preliminary report), *Jr Am Med Assoc*, 1944, cxli, 24
- 24 PASCHKIS, K E, CANTAROW, A, RAKOFF, A E, WALKING, A A, and TOURISH, M J Thiourea and thiouracil in treatment of thyrotoxicosis, *Jr Clin Endocrinol*, 1944, iv, 179
- 25 (a) Leading Article, Treatment of thyrotoxicosis with thiourea, *Lancet*, 1943, ii, 483  
(b) Leading Article, Anti-thyroid substances, *Lancet*, 1943, ii, 197
- 26 HIMSWORTH, H P Thyrotoxicosis treated with thiourea, *Lancet* 1943, ii, 466
- 27 Proceedings of the Meeting of the Johns Hopkins Medical Society NEWMAN, ELIOTT V, RIENHOFF, W F, JR, and RICH, A R Symposium on the use of thiouracil in hyperthyroidism, *Bull Johns Hopkins Hosp*, 1944, lxxix, 153
- 28 RAWSON, R W, EVANS, R D, MEANS, I H, PFACOCK, W C, LERMAN, J, and COPTILL, R E The action of thiouracil upon the thyroid gland in Graves' disease *Jr Clin Endocrinol*, 1944, iv, 1
- 29 WILLIAMS, R H, and CLUTE, H W Thiouracil in the treatment of thyrotoxicosis, *New England Jr Med*, 1944, ccxxx, 657
- 30 CAMPBELL, D, LANDGREBE, F W, and MORGAN, T N Pharmacology of thiourea, *Lancet*, 1944, i, 630
- 31 Royal Society of Medicine (Abstract of Discussion) DODDS, E C, SHAPPIY-SCHAFER E P, and EVANS, H Thiouracil in the treatment of thyrotoxicosis, *Lancet* 1944 ii 13
- 32 GABRILOV, J L, and KRET, M I Sensitivity to thiouracil *Jr Am Med Assoc* 1944 cxli, 504
- 33 STONE, H S and SHORR E Metabolic effects of thiouracil in Graves disease *Science* 1944, xciv, 305
- 34 HUGHES A M Cretinism in rats induced by thiouracil *Endocrinology* 1944 xxxiv, 69
- 35 MINNER, J P, LUNIK, E P, and TURNER, C W Effect of thiouracil and thiourea on the thyroid gland of the chick, *Endocrinology*, 1944, xxxiv, 168
- 36 HUGHES, A M, and ASTWOOD E B Inhibition of acromegaly in rats by thiouracil, *Endocrinology*, 1944, xxxiv, 135

- 37 MACKENZIE, J B, and MACKENZIE, C G Effect of prolonged and intermittent sulfonamide feeding on the BMR, thyroid, and pituitary, Bull Johns Hopkins Hosp, 1944, lxxiv, 85
- 38 WILLIAMS, R H, BISSELL, G W, JANDORF, B J, and PETERS, J B Some metabolic effects of thiouracil with particular consideration of adrenal functions, Jr Clin Endocrinol, 1944, iv, 58
- 39 ASTWOOD, E B, and BISSELL, A Effect of thiouracil on the iodine content of the thyroid, Endocrinology, 1944, xxxiv, 282
- 40 RAWSON, R W, TANNHEIMER, J F, and PEACOCK, W The uptake of radioactive iodine by the thyroids of rats made goitrous by potassium thiocyanides and by thiouracil, Endocrinology, 1944, xxxiv, 245
- 41 FRANKLIN, A L, LERNER, S R, and CHAIKOFF, D. L The effect of thiouracil on the formation of thyroxin and diiodotyrosine by the thyroid gland of the rat with radioactive iodine as indicator, Endocrinology, 1944, xxxiv, 265
- 42 WILLIAMS, R H, JANDORF, B S, and KAY, G A Methods for the determination of thiouracil in tissues and body fluids, Jr Lab and Clin Med, 1944, xxix, 329
- 43 WILLIAMS, R H, WEINGLASS, A R, BISSELL, G W, and PETERS, J B Anatomical effects of thiouracil, Endocrinology, 1944, xxxiv, 317
- 44 BAUMANN, E J, METZGER, N, and MARINE, D Mode of action of thiourea on the thyroid gland of rabbits, Endocrinology, 1944, xxxiv, 44
- 45 DEMPSEY, E J, and ASTWOOD, E B Determination of rate of thyroid hormone secretion at various environmental temperatures, Endocrinology, 1943, xxxii, 509
- 46 ROSENTHAL, N, VOGEL, P, and TYSON, M C (To be published)
- 47 ASTWOOD, E B Thiouracil treatment in hyperthyroidism, Jr Clin Endocrinol, 1944, iv, 229
- 48 MCGAVACK, T H, GERL, A J, VOGEL, M, and SCHWIMMER, D The treatment of 26 thyrotoxic patients with thiouracil and a review of toxic reactions in all (135) reported cases, Jr Clin Endocrinol, 1944, iv, 249

# WERNER'S SYNDROME (PROGERIA OF THE ADULT) AND ROTHMUND'S SYNDROME: TWO TYPES OF CLOSELY RELATED HEREDOFAMILIAL ATROPHIC DERMATOSES WITH JUVE- NILE CATARACTS AND ENDOCRINE FEATURES; A CRITICAL STUDY WITH FIVE NEW CASES \*

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OBSERVATIONS on these rare and apparently heredofamilial disorders are scattered throughout the different branches of medical literature according to the particular interest of the individual author specializing in involvement of the eye or the skin or the nervous system

B S Oppenheimer and V S Kugel (1934) have the distinction of first reporting this condition in American medical literature, renaming it "Werner's syndrome" The characteristics of this syndrome are

- Shortness of stature, characteristic habitus
- Canities (i e, premature graying of the hair)
- Premature baldness
- Scleropoikiloderma
- Trophic ulcers of the legs
- Juvenile cataracts
- Hypogonadism
- Tendency to diabetes
- Calcification of the blood vessels
- Osteoporosis
- Metastatic calcifications
- Tendency to occur in brothers and sisters

The cases published in the literature under different titles have been purposely selected and grouped It seems necessary to quote and discuss in detail the pertinent literature in order to prove the actual existence of Werner's as well as Rothmund's syndrome and to justify their separation Observations of our own cases should show that the classification of the skin changes as "scleroderma" or "scleropoikiloderma" is not appropriate since we are dealing with heredofamilial dermatoses of a special nature The pathogenesis of the ulcers occurring in Werner's syndrome either "trophic" or due to "pressure," will be discussed In addition the relationship of the syndrome under discussion to other clinical syndromes will be demonstrated

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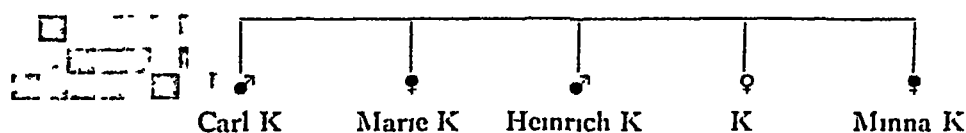
From the Joseph H Pratt Diagnostic Hospital and Tufts College Medical School, Boston, Mass. Aided by grants from the Rockefeller Foundation and the George Horne Trust Fund

- I Werner's syndrome (progeria of the adult)
- II Rothmund's syndrome
- III Cases related to Werner's syndrome (progeria of the adult) and Rothmund's syndrome
  - A Cataracta dermatogenes (neurodermitis) Type Andogsky
  - B Progeria of children (Hutchinson-Gilford's syndrome)
  - C Myotonic dystrophy
  - D Hereditary ectodermal dysplasia of the hydrotic type   Dys-  
trophy of the hair and nails (Type McKay-Davidson)

### I WERNER'S SYNDROME (PROGERIA OF THE ADULT)

In 1904 Otto Werner<sup>1</sup> described in his Doctor's thesis from Ophthalmological Clinic in Kiel, a peculiar disorder, under the title "Cataract in Connection with Scleroderma," occurring in four brothers and sisters, two males 40 years and 36 years old, and two females, 38 years and 36 years old (a fifth sister, 33 years old, was healthy)

Family K



The grandfather and grandmother and parents of the patients lived to an old age. There were no interfamilial marriages and no blood relationship. It was only reported that a cousin of the patients, on the mother's side, already showed graying of the hair at the age of 20.

### CASE REPORTS

**Case 1** *Carl K*, 40 years old. Normal birth. Normal development in childhood. Short in stature. No measures of height were reported. The appearance was atrophic and senile. Hairs started to turn gray at 20. At 40 they were snow white and very scarce. Nothing is reported concerning eyebrows, eyelashes or pubic hair at the age of 20. Areas of hyperkeratosis were first noted under the large toe, under the fifth toe and on the heels. After removal they recurred in a short time. At the age of 40 hyperkeratotic areas were noted over the malleoli, heels, on almost all toes, especially the end phalanx of the left second toe, which was covered with a cap of horny tissue. The skin over the lower extremities and on both feet became thickened at 30. Ulcers appeared at this time, first on the left third toe and on the skin of the dorsal surface of both feet. The ulcers were as large as a dime. Later ulcers developed on the external malleoli and on the skin over both Achilles tendons. In almost all instances areas of inflammation were observed, especially on the dorsum of the feet. These places were so painful that the patient cried like a child. The taut skin was stretched over the underlying structures which were lacking in subcutaneous fat. In some places blue scales covered the shiny, thin skin. The skin changes were only noted on the lower legs and feet. Because of the tightness of the skin motion in the ankle and phalangeal joints of the feet was considerably restricted. There were no hair in the affected areas. Unlike his brother the patient did not complain of

pain in his legs. The *muscles and subcutaneous fat tissue* on both lower legs were underdeveloped. On the forearms and hands also, muscles as well as subcutaneous fat tissue were atrophic, but to a lesser degree than on the lower legs and feet. The *toe-nails* were lacking on the left third and fourth toes and on the other toes the nails were atrophic. A similar condition of the nails was noted on the right foot. There is no report on the character of the *voice*. *Cataracts* developed at the age of 28 and were operated upon at the age of 36. *Endocrine features*. Other than the senile atrophic appearance there was no report on the sex organs or his sexual life. The fact that he was not married hints at a sexual deficiency.

*Case 2 Marie K*, 38 years old. Normal development as a child. She was very short in *stature* and gave the general impression of being an underdeveloped, degenerated person, with thin muscles and very little subcutaneous fat tissue. *Hairs* were fine, gray and scarce. *Psyche* and intelligence were normal. *Skin*. At the age of 22 the patient noted that the skin of both lower legs and feet had already become taut and fixed on the underlying structures. The veins under the thin atrophic skin became visible in their smallest ramifications. There were no hairs on the affected parts of the skin. Because of the tightness of the stretched skin motion of the ankle joints and phalangeal joints was almost impossible. The color of the skin was normal, except that the face had a reddish hue due to severe acne. When she was 32 an ulcer developed on the skin covering the left outer malleolus which did not close for two years. When she was 34 an ulcerative skin defect, the size of a walnut, located on the left lower edge of the shin bone, which, after several years, had not yet healed. At the time this 38 year old patient was first seen the skin of both lower legs was taut, glossy and atrophic. The skin on the affected parts showed patches of grayish brown discoloration beside normal skin of normal color. Slight scaling was noted on sharply defined places where the normal skin bordered the affected parts. Areas of thick *hyperkeratosis* were present over both heels, under the large toes, on the lateral sides of the feet and on the *dorsum pedis* on several toes. Ulcers and scars of ulcers were seen on all parts exposed to pressure on both lower legs. Especially large ones were located over both *Achilles tendons*, on both shins on the malleoli and on the lateral sides of the feet and on the back of some toes. On the large toe of the left foot only a rudimentary nail had developed. On all other toes of the left foot nails were lacking. Of special interest was the severe involvement of the skin of both lower arms and hands. The thin, reddish, atrophic skin over both hands was so tightly stretched over the bony structures that the first and second phalangeal joints on all fingers were ankylosed. The patient could not move her fingers. The fifth finger of the left hand was contracted in flexed position. Defined areas of hyperkeratosis similar to the condition on the feet were noted over the metacarpophalangeal and over some interphalangeal joints. The finger-nails were normal except that of the left fifth finger which was atrophic. The muscles of both lower arms were atrophic and meager. The subcutaneous fat tissue was almost lacking on both lower arms and hands. Tendon reflexes were normal. *Cataracts* developed on both lenses at the age of 23. The cataracts matured six years later and were successfully operated upon. *Endocrine features*. The thyroid gland was enlarged to the size of a fist. The patient did not complain of palpitation or other symptoms of hyperthyroidism. Menstruation had started at the age of 13 and had been regular until the age of 20. Thereafter the patient menstruated only twice a year for a few years, then menstruation ceased altogether.

*Case 3 Heinrich K*, 36 years old. He was a farmer and was able to work until his eyesight deteriorated at the age of 33. As a child his development was normal. No record of his height was reported. At the time of his first examination his appearance was senile. After he graduated from high school his hair began to turn gray. At the age of 24 all the scalp hair was grayish. There was no report of the

presence or absence of pubic hairs His bony structure was very thin The skin was of senile texture and shrivelled A withered condition was especially noted on the skin of the face Tightness of the skin in Heinrich K was observed only on both feet and the lower third of the lower legs The skin in these areas was taut and atrophic and of a reddish hue Some areas of the feet were puffy and itching Slight scaling on some areas was noted The mobility of ankle and phalangeal joints was not restricted Only over the olecranon of the right elbow circumscribed areas of *hyperkeratosis* were seen Ulcers were present only on two areas, namely, on the skin over the right malleolus and over the medial side of the large toe Cataracts developed at the age of 29 The patient was operated upon at the age of 33 The arterial blood vessels exhibited definite signs of arteriosclerosis *Endocrine features* Other than his senile, atrophic appearance no remarks concerning endocrine symptoms were made

*Case 4 Minna K*, 31 years old Her development in childhood was normal At the time of her examination she gave the impression of a degenerated and infantile person She was of *very short stature* Her *psyche* was abnormal She cried and laughed without reason She was suspicious and refused at first to be examined Her scalp hairs were entirely gray The first skin changes were observed at the age of 22 The skin over the second and third left toes became thickened and covered these toes like a horny "capsule" After the horny layer was removed an ulcer remained Both toes had to be amputated Two years later the same condition resulted in the amputation of the fourth left and second right toes At the time of her examination, at the age of 31, both feet were deformed because of the previous operations The arches were abnormally high Exostoses were present on lateral parts as well as on the dorsal parts of the feet There was slight scaling of the skin over the lower legs and feet and it was taut and atrophic, but of normal color The skin was so tightly stretched over the bony structures of the feet that the mobility in both ankle joints was almost completely restricted Numerous telangiectases of the skin covering the malleoli and the exostoses were noted Areas of *circumscribed hyperkeratosis* were outstanding on both heels and over the exostoses The nails of the two remaining toes of the left foot had completely disappeared, the end phalanges of these toes were atrophic The nails of the four remaining toes of the right foot were present only in rudimentary form The muscles of both lower legs were extremely thin and underdeveloped The panniculus adiposus in this part of the legs was almost completely absent Although the bony structures of the whole body were extremely thin and fragile, spontaneous fractures had never occurred Cataracts developed at the age of 27, first on the right eye and, two years later, on the left eye *Endocrine features* The thyroid was enlarged forming a goiter the size of an apple No signs of hyperthyroidism were noted During her adolescent years the menstruation was rare and scanty At the age of 19 the menses stopped completely. Her presenile appearance was outstanding

*Comment* There is no question that Werner's observations on four brothers and sisters represent the first description of a unique clinical entity Werner, a medical student in the ophthalmological ward, was concerned chiefly with the juvenile cataracts, but the description of the appearance of these patients, especially the detailed appearance of the skin changes, at once gives the impression that the described disease is of general medical interest and significance since it involves not only the eyes but the whole body All the symptoms of these brothers and sisters developed during the second and third decades of life Birth was normal development in childhood was

normal, but in the adolescent age they remained short in stature. It is remarkable how similar, almost to the last detail, the other features likewise appeared in these patients. They became gray around the age of 20, later the skin on the lower legs became taut, atrophic and stretched over the underlying tissues, which consisted of a very meager subcutaneous fat tissue and thin atrophic muscles. Areas of circumscribed hyperkeratosis were painful and after the horny layer was torn off or removed by the pressure of shoes or clothes ulcers resulted. At the same time, in the second decade of life, cataracts developed in both eyes. The whole appearance became more and more senile. The patient became incapacitated for heavy work, partly owing to the immobilization of the ankle joints and feet as a result of the tightness of the skin and the ulcers, and partly owing to general weakness and to the reduced nutritional status of the whole body. Signs of arteriosclerosis became evident and completed the picture of presenility.

Werner has classified the skin changes as scleroderma because the skin of these patients in the affected areas was taut and tightly stretched over the underlying tissues, as in true scleroderma. He did not consider that the circumscribed hyperkeratosis and ulcer formation are not observed as features of true scleroderma nor did he make biopsies to prove his classification histologically. Unfortunately this designation, as will be noted, was used in similar familial cases later published. On the basis of our own observations an effort will be made to classify the nature of the skin changes simulating scleroderma in Werner's syndrome. Werner, himself, relates the observations made on the four adult members of the family K to observations published by Rothmund 61 years ago, describing young people of three different families in whom peculiar skin changes, together with cataracts, occurred. The difference and the relationship of the syndromes described by Rothmund on the one side and by O. Werner on the other will be pointed out in the second part of this paper.

*A. Possius*,<sup>2</sup> in 1920, reported two cases with scleroderma and cataract.

*Case 1* was a 57 year old, intelligent woman, with a small skull. The scalp hair was snow white and scarce. Proptosis of the eyes was noted. The voice was high pitched and hoarse. Scleroderma developed at the age of 20 and bilateral cataracts at the age of 31. No similar disorder in the family was reported.

*Case 2* was a 35 year old male who was short in stature. The muscles and adipose tissue were underdeveloped. The voice was high pitched and hoarse. Scleroderma started at 20 and cataract at 30. One sister was reported to be of the same small stature as the patient.

*G. Guillemin, J. T. Majonandre and R. Marquigny*<sup>3</sup> (1923) reported a male patient 28 years old, under the title "Sclerodermie progressive avec cataracte double precoce chez un infantile."

No other members of the family were afflicted. He was short in stature (118 cm) and his growth stopped at the age of 10. The extremities were short and thin in contrast to the chest and abdomen. Hands and feet were small. The fingers showed nodular deformities as in arthritis. Hair: Face and chin were hairless with the exception of a few fine mustache hairs. Pubic hairs were scarce and of a female distribution. The skin was tight and not pliable on the lower part of the legs.



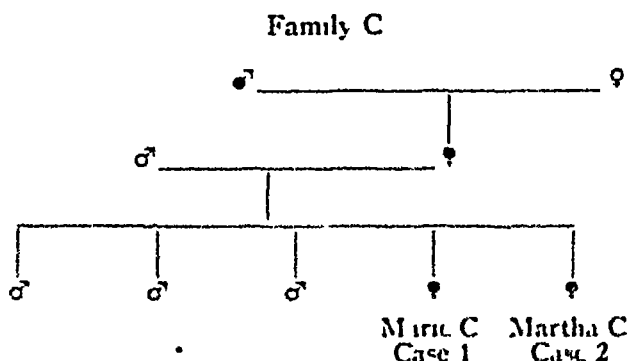
especially on the toes. The skin was fine in texture on the dorsum of the feet. Under the great toes, areas of *hyperkeratosis* were found. *Ulcers* were also present under the great toes as well as on points of pressure. The muscles on the lower part of the legs were atrophic. Above the knee the *muscles* were normal. On the face, chin and arms the *skin* was also tight but less so than on the feet. There was some difficulty in opening the mouth wide. No telangiectases were noticed. *Cataracts* developed in both eyes when he was 25. The *voice* was harsh and high pitched. The *heart* was normal. Blood pressure was 140 mm Hg systolic and 90 mm diastolic.

*Endocrine features.* Gynecomastia of both breasts. Although the genital organs were very small and the testes were only the size of those of a 10 year old boy the patient claimed to have had intercourse three to four times in a single night. He had married at the age of 24 but had no children. Sella turcica was normal. Roentgenograms of the bones showed the epiphyseal fuses closed.

*N Manjukowa*,<sup>4</sup> in 1923, in a paper concerning the relation of cataract to endocrine disturbances, described a 36 year old man whose features apparently belong to the syndrome under discussion, whereas a patient, reported in 1922 by *C Papasiatyakis*,<sup>5</sup> with complete alopecia, atrophy of the nails and cataracts, should not be registered as Werner's syndrome but rather as "hereditary ectodermal dysplasia."

*E M Barbot*,<sup>6</sup> in a Thèse of Paris, in 1925 (the same cases were later republished by *Momer-Vinard and Barbot*<sup>7</sup>) discussed in a paper entitled "La sclerodermie associé à la cataract (affection familiale)" a family in which the *grandfather* had early canities, and *cataracts* at the age of 40. The mother observed graying of the hair at the age of 20 and cataracts between the ages of 20 and 30. She did not have any skin changes. This woman had five children. One child died of intestinal troubles. Two sons were healthy. Two daughters showed skin changes, canities and cataracts.

*Case 1.* Miss Marie C, age 46, height 160 cm. Shell-like plaques of *hyperkeratosis* on both soles beneath the great toe were noticed at the age of 20. The *skin* over the lower legs and ankles was tightly stretched. At the age of 22 the *voice* became hoarse. She was a singer and had to give this up. At the same time the



scalp hair began to turn gray and to become sparse. The pubic hairs almost disappeared. When she was 25 *cataracts* developed. At the time of the last examination, 1931, the skin over the ankles and feet was taut and tight. She had difficulty in moving. On the points of pressure on both lower legs *ulcers* and scars of *ulcers* were present. Both lower legs were very thin, almost like a skeleton (*Cadaveric contracture*). Above the knees skin was normal and the muscles better developed. Toenails were atrophic. Menstruation started at 12 and stopped at 44. Tendon reflexes of the lower extremities could not be elicited. Triceps were normal.

*Case 2.* Miss Martha C, 42 years old. Short in stature. The *skin changes* developed at the age of 25. The *ulcers* are the same even in small details, as seen

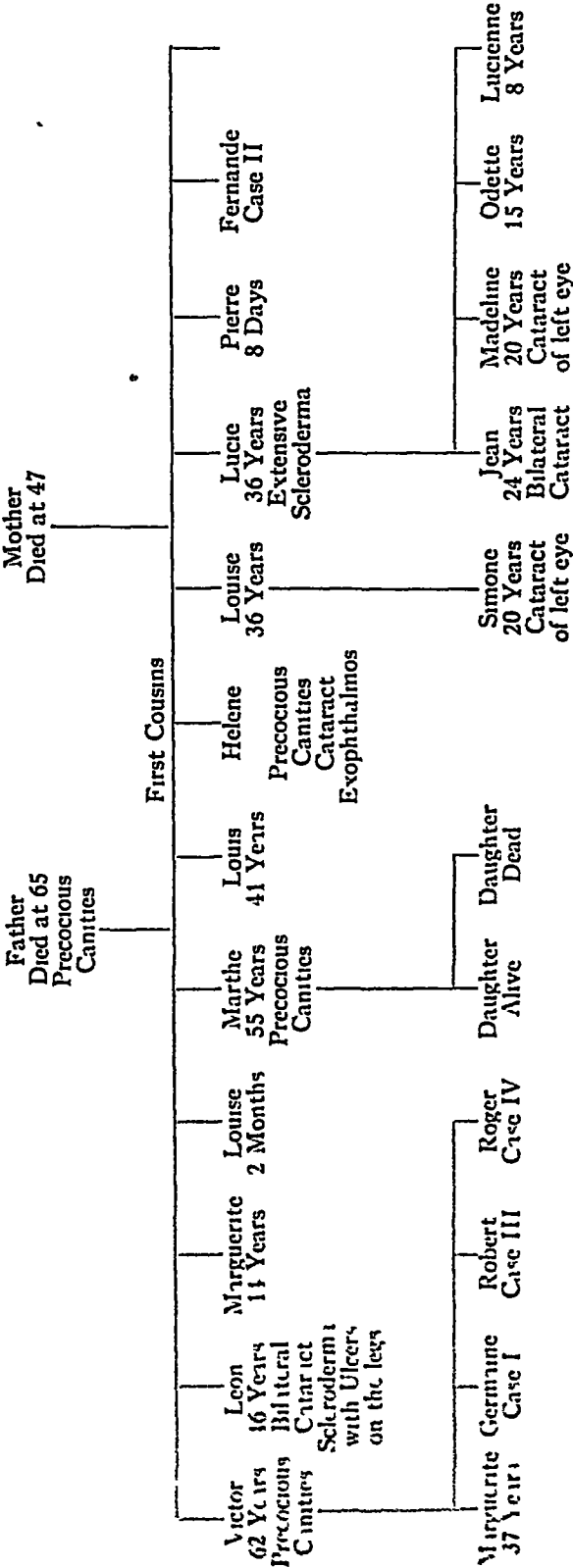


FIG 1

in her sister. When she was 30, bilateral *cataracts* were evident. Menstruation began at the age of 13 and was still regular at 42. Her voice was clear.

*S. Bau-Prussak*<sup>8</sup> reported in 1926, in his paper entitled "La dégénérescence génito-sclérodermique," the case of a 36 year old woman. At the age of three the patient's vision was defective. Menstruation started at 18 and stopped at 20. The general habitus of the patient was underdeveloped.

*M. Sainton and Mamou*<sup>9</sup> described, in 1927, under the title "Syndrome pluriglandulaire avec sclerodermie et cataracte" a 25 year old male metal worker. He had only one brother who was normal. He was short in *stature*, 149 cm. He looked much younger than his age. *Hairs* were rare and gray, there was no mustache.



FIG 2 Case 1 Germaine. Gray scarce scalp hairs, scanty eyebrows, no eyelashes. Presenile appearance.

Eye brows and eyelashes were sparse as were, also, the pubic hairs. The *nails* stood out from the head and were flat. The *skin* was of waxy color, thin and adherent to the underlying tissue. The motion of both feet was inhibited by the taut, sclerodermatous skin. On the feet were several *ulcer* scars. On the right great toe an active ulcer was present. In contrast to the globulous abdomen the extremities were slender and thin. The toe-nails were atrophic and deformed. Bilateral *cataracts* developed at the age of 22. The *voice* was hoarse. *Endocrine features*. The penis was small. The testes descended at the age of 13 and were small in size. *Sella turcica* was normal in size. The thyroid was difficult to palpate. There was gynecomastia of the right breast.

*T. Hashimoto*<sup>10</sup> reported, in 1930, the case of a 44 year old man who developed cataracts and scleroderma. Penis, testes and epididymis were very small.

*H. Eguchi*<sup>11</sup> published, in 1930, two isolated cases, without history of familial incidence, which belong to this group. A 32 year old man and a 30 year old woman had identical symptoms. 1 Disturbance of growth, height 148 cm. 2 Scleroderma-

like skin changes on hands and feet 3 Canities (grayness of the scalp hair)  
 4 Cataracts showed at the age of 28 in the man and at the age of 26 in the woman,  
 star-like densities on the posterior cortex of the lens 5 Hoarse voice 6 Re-  
 tardated development of the sex organs in both cases 7 Both patients had high  
 blood sugar values In addition a goiter was present in the female

The cases reported by *A Sésary, Favory and H Mamou*,<sup>12</sup> published also in his  
*Thèse de Paris, 1931*, by *H Mamou*<sup>13</sup> alone, under the title "Some rare symptoms  
 of scleroderma" do not belong to the group of Werner's syndrome They do not  
 show shortness in stature, canities, ulcers or presenility, but true scleroderma with  
 melanosis of the skin and cataracts



FIG 3 Shell-like hyperkeratosis on both heels, under the large toe. Ulcers under  
 the fifth toe, hallux valgus

The most impressive evidence of the heredofamilial occurrence of the syndrome  
 under discussion is found in the description of *E Krebs, E Hartmann, and F*  
*Thiebaud*<sup>14</sup> of "un cas familial de syndrome de sclerodermie avec cataracte, troubles  
 endocriniens et neurovegetatifs associés"

*Case 1 Mrs Germaine G, née P, 35 years old married, no children Short*  
*stature, very slender, scanty gray hair in contrast to her young appearance Scalp*  
*hairs started to turn gray when she was 18 There were almost no eyebrows and*  
*only a few eyelashes Secondary pubic hairs were short and straight Skin Sclero-*  
*derma developed slowly without premonitory edema on the lower legs and feet The*  
*hue of the skin was waxy For a long time the patient had been able to walk only*  
*with difficulty because the skin was very tightly stretched over the ankles and the*  
*dorsum of the feet The feet gave the impression of solid blocks The skin over*  
*both Achilles tendons, over both heels and on the soles under the large toes and*  
*circumscribed areas of extreme hyperkeratosis of a corn-like nature After the*  
*hyperkeratotic areas peeled off, deep non-healing ulcers developed Both large*  
*toes were in hallux valgus position The insteps were very high and the toes were*  
*fixed in extensor position The reflexes were normal Contracture of both eyes Opera-*

tion performed on cataract of the right eye. There was slight exophthalmos, slight tremor of the hands. The thyroid was not enlarged. *Endocrine features* Menstruation was always irregular. It started at 12. There were complaints of hot flashes. Basal metabolic rate +11. No disease of internal organs found. Fasting blood sugar, 88 mg per cent. Sugar tolerance curve was normal. Cholesterol 170 mg per cent, calcium 11 mg per cent. There was no report of roentgenograms of the blood vessels or bones.

*Case 2 Miss Fernande P*, 38 years old, aunt of case 1. Short in stature. Presenile appearance. Hair was already gray at 18. There were almost no eyebrows or eyelashes. Pubic hairs were very scarce and straight. *Skin* The same

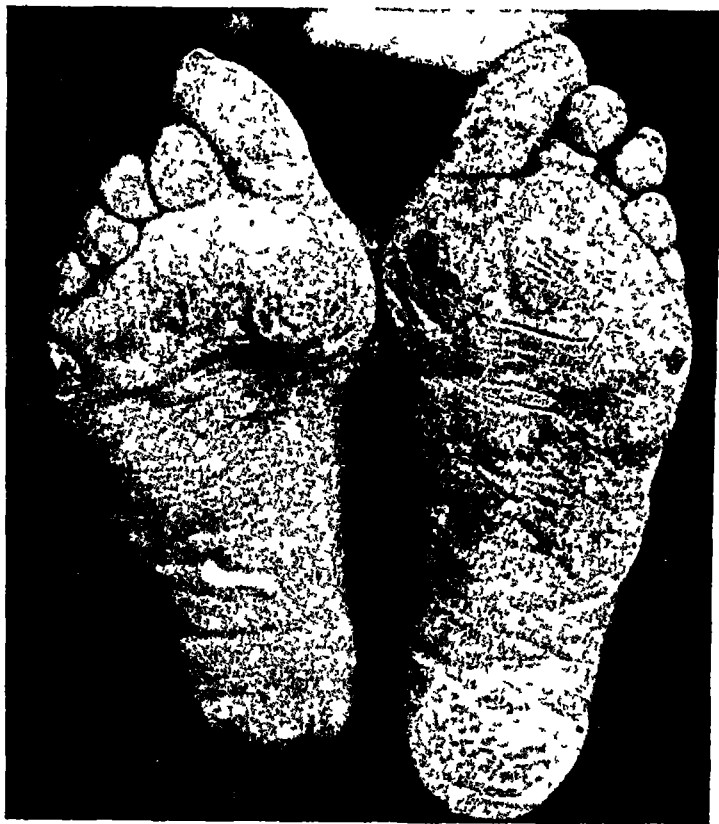


FIG 4 *Case 2 Fernande* Note same areas of hyperkeratosis only this time small ulcer under left toe

changes with circumscribed hyperkeratosis and ulcers as described in case 1 were found. The phalanges of the toes were fixed in a flexed position in contrast to the extensor position of case 1. Both large toes were in hallux valgus position. The skin was more scaly and itching. Bilateral *cataracts* were operated upon at the age of 30. *Endocrine features* Slight exophthalmos. Palpitation at a rate of 100 was noted. Thyroid was not enlarged. Basal metabolic rate +16. Menstruation was regular. Mammæ very small. Hot flashes. Sella turcica normal in size. *Vascular system* Heart—no disease was noted. Roentgenogram showed the aorta distended and slightly sclerotic. Wassermann reaction was negative. Fasting blood sugar, 88 mg per cent. Sugar tolerance normal. Total cholesterol 260 mg per cent.

*Case 3 Robert P*, 29 years old, brother of Germaine, case 1. Short in stature, 151 cm. Weight 45 kg. Gray, scarce scalp hairs. Pubic hairs very rare. Body hairless. The nose was beaked. The chin was small and retracted. The ears were



FIG 5 Skin tightly stretched over ankles and toes Note healed ulcer under the left malleolus



FIG 6. Case 3 Robert Large ulcer on left inner malleolus

very small, the auricles were flat but projected from the head. The skin over the forehead was taut, without folds. The skin on the forearm and hands was tightly stretched. The hands were small and the fingers were short and crooked and of nodular appearance. A similar shape of the fingers was also observed in cases 1 and 2. The skin over the lower legs and feet was atrophic and of waxy appearance.

The skin on these parts was so tightly stretched that any motion in the ankle joints was difficult. The underlying *muscles* were so thin they gave the lower legs and feet a skeleton-like appearance. Both large toes were in hallux valgus position. The toes were fixed in extension position. Numerous *ulcers*, old and new ones, were present on the points of pressure. An especially large ulcer was located on the inner malleolus. A few telangiectases were observed on the base of the thorax. *Cataracts* were present in both eyes. The *voice* was hoarse and high pitched. *Endocrine features*. The thyroid was not palpable. Genital organs were small and underdeveloped. The right testicle was ectopic, the left testicle was small. Genital functions were reported as normal, but probably developed late. *Vascular system*. The heart was reported as normal. Pulse rate was 90. Blood pressure was 130 mm Hg systolic and 80 mm diastolic. No report of calcification in the arterial wall was made. The *spleen* was of normal size. Tendon reflexes were normal, as was the sensibility. Fasting blood sugar, 116 mg per cent. Sugar tolerance test produced glycosuria. Sugar tolerance curve was that of a potential diabetic. Calcium 99 mg per cent. Total cholesterol 90 mg per cent. Basal metabolic rate +13.



FIG 7 Case 4 Roger. Small hands, deformed phalangeal joints. Presenile appearance.

*Case 4 Roger P* is the tallest of his family—167 cm. He presented the same general presenile aspect as his brother. The forehead was smooth, without wrinkles, the nose was thin, the chin was small and retracted, the ears were flat and projecting. The face resembled that of a mummy. The *skin* had features similar to those of his brother Robert, but to a lesser degree. Scars of *ulcers* were visible on the points of pressure (over elbows, heels and ankles). On the lower part of the thorax the skin showed the same telangiectases as did that of his brother. Scalp *hairs* were of an indefinite grayish color and scarce. Eyebrows were present. Pubic hairs were

almost absent *Cataracts* were developing in both eyes *Teeth* showed malformation, especially on the superior incisors *Endocrine features* The penis and the testicles were very small *Puberty* was late *Intercourse* was sometimes carried out *Slight exophthalmos* *Vascular system* The heart was normal *Blood pressure* was 130 mm Hg systolic and 80 mm diastolic *Pulse rate* was 102 The skin changes were the same as in all the cases reviewed above and characteristic for the heredofamilial dermatosis in Werner's syndrome, but not of true scleroderma All cases examined of family P were short in stature and abnormally lean Especially the lack of subcutaneous tissue in the distal parts of the extremities gave the lower legs a skeleton-like appearance *Hallux valgus* formation was noted in all members of this family *Hands and feet* were abnormally small and short The chin was small and retracted The small size of the hands and feet and the small retracted chin, in contrast to their large size in acromegaly, is justifiably called *acromicria* *Slight exophthalmos* with and without goiter formation, but without definite signs of hyperthyroidism is reported in some members of family P *Hypogonadism*, however, is observed in all four cases exhibiting the complete syndrome under discussion

*Comment* In addition to these four cases of the family P, examined by the authors personally, the history of the whole family is revealed in the family tree

The syndrome under discussion was present in all its features in three members of the second generation (Leon, Louis, Fernande) and in three members of the third generation, but some features of the syndrome (canities, scleroderma-like skin changes and cataracts) occurred interchangeably as abortive features (*forme fruste*) also in other members of the family in three generations These observations are of great importance since they prove first, a recessive inheritance of the syndrome, second, that abortive features of the syndrome may occasionally occur as "*forme fruste*" easily overlooked by physicians not familiar with this peculiar heredofamilial disorder

B S Oppenheimer and V H Kugel<sup>15</sup> reported, under the title "Werner's syndrome," three cases with photographs and the autopsy findings Two of these were brothers

*Case 1* D G, male, 48 years old *Grandparents and parents* were first cousins *Stature* was short, height 149 cm *Weight* was 118 pounds At the age of 12 premature graying of the scalp *hairs* and loss of scalp hair were noticed At 48 he was bald, only sparse hairs being present on the scalp *Pubic hairs* were sparse. *Chest hairs* were abundant, but gray On the extremities hairs were absent and sweating was diminished The *skin* of the entire face, part of the scalp and back of the ears was distinctly abnormal but not so markedly altered as in the extremities The normal luster, smoothness and pliability were replaced by thickening, roughness and loss of normal elasticity The mouth was abnormal, small, surrounded by fine rhagades, and could not be opened easily In the extremities the changes were most marked distally and gradually regressed to merge imperceptibly into apparently normal skin, at the upper third of the legs and forearms There were circumscribed areas of *hyperkeratosis* on the plantar surfaces of both feet and over the very taut scar at the site of the amputation of the left foot The skin of the feet was atrophic, smooth, glistening and taut and impeded the motion of the joints of the toes There was an edematous appearance of the feet, but no pitting on pressure There were numerous scars of old ulcerations, some surrounded by areas of pigmentation, over



both malleoli and plantar surfaces of the toes. There was an indolent, non-erythematous ulceration, the size of a quarter, over the right external malleolus, and there were several other ulcerations around the right ankle and over the dorsal surface of the toes of the right foot. There were also a few fine telangiectases. The skin of the hands and fingers was more typically "sclerodermatous." It was thickened, wrinkled, in places adherent with marked loss of elasticity. Over the olecranon were patches of hyperkeratinization. On the forearm the skin was atrophic and taut. The nails of the toes showed advanced atrophic changes, i.e., hyperkeratinization, deformation and discoloration. The nails of the fingers were brittle and revealed numerous longitudinal striations. *Biopsy of the skin* "shows marked atrophy of the epidermis. Papillae are flattened. Underlying tissue is hyalinized. Calcium stain is negative. Histological picture is consistent with the diagnosis of scleroderma" (Dr Perla). *Joints* The small joints of both feet were immobile owing to the taut skin stretched over them. There was limited motion of the ankle joints. There was normal mobility of the larger joints of the body. Left foot showed productive arthritis. Small exostoses were present. Both feet were flat and everted with

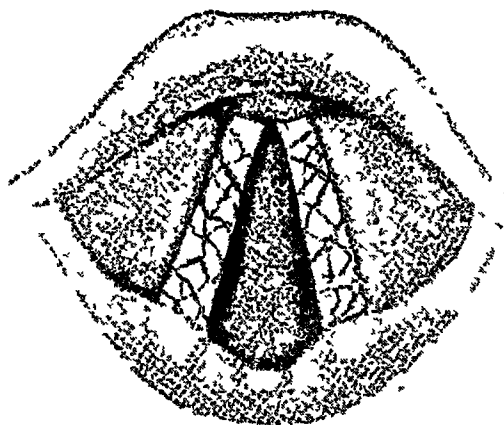


FIG 8 Picture of vocal cords (Reproduced from B S Oppenheimer and V R Kugel)

hallux valgus formation. The contrast between the well developed chest and trunk and the thin, slender "juvenile" extremities was striking. The bones of the arms and legs were thin. The subcutaneous fat and the muscles were underdeveloped (especially on both lower limbs and forearms, according to the photograph). *Osteoporosis* of the osseous system was seen by roentgenogram. *Blood vessels* Calcification of the medium-sized arteries was visible in different parts of the extremities in roentgenograms. *Eyes* *Cataracts* in both eyes had been operated upon. The cataracts developed at the age of 36. *Teeth* were normal and not decalcified. *Voice* was high pitched and husky. *Larynx* (S R Kramer) "Overhanging epiglottis. On the upper surface of the vocal cords there are white areas, irregular in size and shape, separated from one another by bands of varying width of pinkish red mucosa. These reddish strands are made up of dilated vessels in the midst of congested mucosa and extend into the ventricles and on the free edges of the vocal cords. The whole picture is a bizarre one of variegated shape and color. There is slight thickening of the edge of the right cord in its midportion, due to an area of injection." *Vascular system* The patient complained of precordial pain relieved by nitroglycerin. A blowing systolic murmur was heard over the cardiac area. Blood pressure was 168 mm Hg systolic and 90 mm diastolic. Roentgenogram showed cardiac enlargement and

calcified deposits in the arch of the aorta *Endocrine glands* The thyroid was not enlarged Basal metabolic rate was  $-12, -19, -5$  Fasting blood sugar was 85 mg per cent Sugar tolerance test showed a flat curve No glycosuria Blood calcium was 9.9–10.0 mg per cent, phosphorus 2.5–4.2 mg per cent, phosphatase 7 Bodansky units Calcium balance was normal Testes were normal in contour and consistency, but reduced in size The penis was underdeveloped Libido and potency were claimed to be normal Neurologic status showed no abnormality

*Case 2* A G, a 30 year old man, brother of D G, was short in *stature* Height was 147 cm, weight 131 pounds In general appearance he resembled his brother so closely that they were often taken for twins Although six years younger than his brother, on the whole he looked older The general habitus, premature senility, thin, slender extremities, flat and everted feet, hallux valgus formation, were the same in both patients Scalp *hairs* started to turn gray at the age of eight At the age of 20 he began to lose his scalp hair and at 22 he was noticeably bald Hair over the chest and abdomen was sparse The distribution of the pubic hair was feminine in type *Skin* Although the distribution of the changes of his skin was identical with that of his brother, the predominating features were atrophy and telangiectases, so that dermatologists, from inspection of his skin alone, would emphasize the poikilodermatous rather than sclerodermatous character of the change, whereas in his brother the scleroderma predominated In his lower extremities he also presented cutis marmorata The ulcerations were more numerous, more extensive and more persistent than those of his brother There was a shallow ulcer, due to pressure, over his left elbow, about 3 cm by 1.5 cm, exposing the periosteum Telangiectases on knees and scrotum were prominent He was admitted to the hospital several times because of his ulcers Secondary infection and cellulitis made an amputation of the right big toe and metatarsal bone necessary *Skin biopsy* (S M Peck) "The epidermis is thin throughout most of the section The normal rete pegs have disappeared There is a moderate hyperkeratosis with no parakeratosis The epidermis has for the most part been reduced to six layers The stratum granulosum is only one layer thick The basal cell layer shows scattered areas of edema, many of the cells are reduced in size, seem shrunken, whereas others show intracellular edema and even formation of vacuoles in the cytoplasm Many of the basal cells contain a fairly good amount of melanine arranged in 'cap' formation over the nuclei No dendritic cells are seen The papillary bodies are flat Scattered through the upper layers of the cutis are a few dilated capillaries with very little, if any, perivascular infiltration consisting mostly of lymphocytes The sebaceous and sweat glands are reduced in number but appear unchanged The cutis is very poor in cellular elements The elastic tissue has mostly disappeared and where it is present it is fragmented and torn In places the collagen fibers themselves take a basophilic stain and seem to have undergone degenerative changes The sections certainly seem to fit in with the picture of poikiloderma atrophicum But there are also some elements which fit in with the picture of scleroderma, especially the atrophic stage of that disease The histologic picture which I have described seems to parallel that of Bloch in his cases" *Joints* Lower and upper extremities, especially on the phalanges of the small hands and feet, ankles and wrists, showed productive arthritic changes similar to those of his brother Slight arthritic changes were also seen on the roentgenograms of pelvis and spine *Osseous system* Diffuse osteoporosis like that of his brother *Blood vessels* Calcification of the medium sized arteries, in different parts of his extremities, was even more marked than in the roentgenograms of his brother *Cataracts* had developed in both eyes The left eye had already been operated upon Marked proptosis of both eyes was noted, without signs of hyperthyroidism He lost 20 *teeth* in the last year, the remaining teeth were loose owing to absorption of the alveolar bone rather than to caries The *voice* was high pitched and husky like that

of his brother. Also the bizarre and characteristic *laryngoscopic picture* was the same as in his brother. *Vascular system* Blood pressure was 140 mm. Hg systolic and 90 mm diastolic to 170 mm systolic and 100 mm diastolic. Electrocardiogram showed left axis deviation but no other changes. On his first admission no enlargement of *liver and spleen* was found. On his third admission liver and spleen were found to be greatly enlarged. Ascites was present. The diagnosis of a hepatic neoplasm was made and verified at necropsy. *Endocrine features* The thyroid was not enlarged. Metabolic rate was between -24 and -6. Fasting blood sugar was 153 mg per cent. Sugar tolerance curve was characteristic of potential diabetes. There was no glycosuria. Blood calcium was 10.6-13.1 mg per cent. Hamilton test was positive. Blood phosphatase showed 4-8 Bodansky units. Calcium balance was within the range of normal. Both *testes* were small. Hypogonadism was evident. In contrast to his brother he was of normal intelligence. The patient died of a terminal pneumonia. The *autopsy* confirmed the diagnosis of a primary liver carcinoma and is reported in detail in B. S. Oppenheimer and V. H. Kugel's paper<sup>10</sup>. The chief abnormal findings were calcification of the mitral and aortic valves, diffuse arteriosclerosis of Monckeberg's type, status after bilateral cataract extraction, diffuse osteoporosis, moderate metastatic calcification in skin, kidneys and vessels. Endocrine glands (examined by D. Marine) "The testes, seminal vesicles and prostate gland were very small. The aspermatogenesis and atrophy of the testes were premature. The adrenals are large with multiple cortical adenomata, the glomerular zone is active (whereas the glomerular zone in older people is usually ill-defined). The thyroid must have passed through cycles of increased and decreased activity to account for the multiple adenomata. The pituitary showed no abnormality. Parathyroids showed increased activity." Skin showed the same findings as reported in the previous biopsy.

*Case 3* H. T., male, 38 years old. *Parents were first cousins*. The father's sister had a daughter with short extremities. The patient was born in Hungary in a district not far removed from the place where the ancestors of both brothers (case 1 and case 2) lived, but the families were not related as far as could be ascertained. He was well until 1926. Injury to his left heel caused a foot drop. At this time he developed various cracks in the skin of the foot which took a long time to heal. By 1937 *ulcers* of the left foot appeared with shortening of the Achilles tendon. In 1937 he had an ulcer on the right heel. The toes of his feet gradually became immovable and the skin became hard, dry and shiny. In 1937 a new growth on the radius of the left forearm was detected. The mass was removed in 1938 and histologically diagnosed as fibrosarcoma. *Appearance* Although actually 38 years old, he was generally taken for 45. He was short in *stature*. His height was 157 cm, his weight 52 kg. The same bizarre discrepancy in the size of the large and even fat torso and the thin and gracile extremities could be seen in the published photograph. The hands were very small. The graying of the hair began at 18. At 38 he was partly bald and gray. The hair over the chest and abdomen was sparse. The distribution of pubic hair was feminine in type. The *skin* was drawn tightly over the shins and wrists and presented many areas of pigmentation, discoloration and dry scales. There were a few telangiectases of the *skin* over the knees and feet. A foul-smelling necrotic mass overlaid the left radius. A pressure *ulcer* was found over the right elbow and a crusted ulcer was seen over the right malleolus. Severe ulcerations and pigmentations were present on both feet. The skin of the toes was dry, hard and so taut that the toes could not be moved. The left ankle was fixed in extension, the knee could not be fully extended and the right ankle had slight power and movement. There were prominent veins over the thorax and extremities. The *vascular system* showed advanced sclerosis of the blood vessels of the upper and lower extremities. No pulsation of the dorsalis pedis or posterior tibial arteries could be felt.

The heart was not enlarged. There was a systolic murmur over the aortic area. Blood pressure was 180 mm Hg systolic and 108 mm diastolic. Electrocardiogram showed a left axis deviation. The eyes were prominent and staring. The sclerae were blue. There was bilateral postoperative coloboma of the iris. *Cataracts* in both eyes were present. They appeared at the age of 31. The cataract of the right eye was operated upon at the age of 38, the cataract of the left eye was operated upon earlier. The *teeth* began to loosen at the age of 33. The remaining teeth were carious. The *voice* was high pitched. Liver and spleen were not enlarged. *Osseous system*. Generalized osteoporosis was found by roentgenogram. *Endocrine features*. The thyroid was not enlarged. Basal metabolic rate was -5 and -8. Total cholesterol 167 mg per cent, cholesterol esters 111. Fasting blood sugar 87 mg per cent. Glucose tolerance curve was rather flat but within normal limits. Serum calcium was 10.3 mg per cent, serum phosphorus 3.9 mg per cent and phosphatase 6 Bodansky units. Hamilton test was positive. The genitalia were small. The prostate was very small and smooth and felt about one-third normal size. A mild degree of gynecomastia was present.

*Comment*. Oppenheimer and Kugel published a family tree of both brothers D G and A G. Like the genealogic table of the family P reported by E Krebs, E Hartmann and F Thiebaut, the occurrence of the syndrome in some members with incomplete features (*forme fruste*) is evident. In the family G usually canities appeared in members of different generations as the outstanding feature, whereas in the family P reported by the French authors, the juvenile cataracts occurred in members of different generations as the outstanding symptom. The skin changes of the three cases of Oppenheimer and Kugel are designated as "sclerodermatous" as the earlier authors did in their cases, or as "poikilodermatous," especially in the case of the younger brother, A G. The question of the presence of true scleroderma is of great importance, since this type of skin disease was ascribed to a primary hyperfunction of the parathyroids. The present conception of the etiology of true scleroderma is based on the histological picture of skin biopsies which exhibit as characteristic features 1 Homogenization and sclerosis of the subcutaneous tissue, and 2 Inflammatory changes of the arteries of the subcutaneous tissue revealing perivascular infiltration and obliterative vascular changes. Neither of these characteristics was prominent. Vascular infiltration and obliterative changes were absent. The pathogenetic connection of diffuse scleroderma with hyperfunction or hypertrophy of the parathyroids is abandoned in the newer literature in favor of a pathogenesis due to inflammatory involvement of the blood vessels of the subcutaneous tissue. Even if the tight and taut appearance of the skin simulates scleroderma in the cases under discussion the histologic features do not bear out the presence of true scleroderma. In case 2, A G, the histological diagnosis pointed to poikiloderma vasculare. Indeed the lesions with telangiectases are very suggestive of this type of skin disorder first described by Jacobi. B Bloch, however (see page 605), hesitated to designate this skin lesion as identical with real poikiloderma or poikiloscleroderma. It is possible, therefore, only to designate these peculiar atrophic skin lesions

by a simple descriptive name such as "atrophic heredofamilial dermatosis with skin ulcers" It does not seem appropriate to attach a dermatological classification already in use for the designation of well defined inflammatory skin diseases to a heredofamilial disorder

Oppenheimer and Kugel<sup>16</sup> express the opinion that the syndrome described by Rothmund in 1868 is essentially different from the cases of Werner and their own cases We agree with the authors that there are

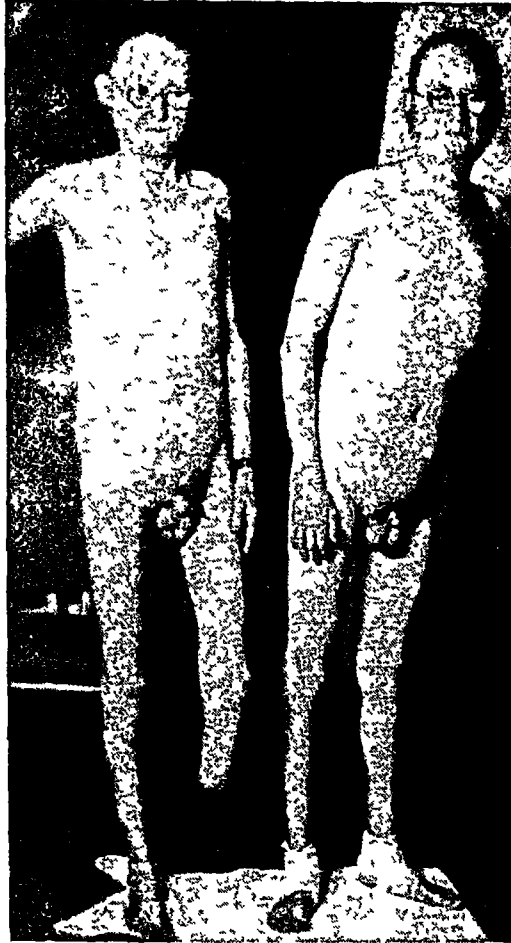


FIG 9 Nathan O and Sidney O Short stature, presenile appearance

definite differences between the adult cases of Werner and the children described by Rothmund, but one is bound to admit that the follow-up study by R Seefelder of Rothmund's cases during their adult life, as well as the later description of other adult cases of Rothmund's syndrome, bears out the close relationship of Werner's and Rothmund's syndrome Further classification of the differences and similarities in Werner's and Rothmund's syndromes will be offered in the second part of this paper

#### OWN OBSERVATIONS

The brothers, Sidney O, 38 years old, and Nathan O, 34 years old, were born in the United States of Russian Jewish parents Both parents were healthy They

came from different towns in southern Russia and were not related. Both paternal and maternal grandparents were healthy and lived to an old age. No interrelationship of any ancestors or any occurrence of a similar disorder in this family is known.

*Case 1* Sidney O. was born a normal child. He went to high school and later to a pharmaceutical school. After graduation he practiced pharmacy. He was very intelligent, well read, and wrote poetry. *Appearance* He was short in stature—five feet three inches (168 cm), weight 120 pounds. There had been no recent weight loss. He looked like an old man, about 20 years older than his actual age. The scalp hairs began to turn gray at the age of 15. They became sparse at the age



FIG 10 Fine, scarce, gray scalp hairs, beaked noses, small mouths

of 20. They now looked like the hairs of a mouse suffering from food deficiency, being fine, sparse and of an indefinite grayish color. He had fine, scarce hairs on the upper lip and on his face. He shaved twice a week. The hairs on his body were scanty and gray. On the lower arms and legs, where the skin changes were most outstanding, there were no hairs at all. On these hairless areas of the extremities perspiration did not occur. The sex hairs were scarce and rudimentary, most of them being straight like bristles. At the age of 21 he noticed circumscribed areas of hyperkeratosis under his big toes, under his heels, on both lateral parts of his feet, as well as on his insteps. At the time of his admission to the hospital these areas of hyperkeratosis were slightly elevated above the surface of the skin and consisted of cornified, horny layers, which gave these areas a shell-like appearance. The patient reported that the removal of these "corns" resulted always in an ulcer which did not heal for a long time. The skin of the face was taut but not tightly fixed on the underlying structures. Beneath the eyes, especially on the nose and nostrils, the skin was not tightly stretched as was seen in true scleroderma. The opening of his mouth was not hampered although the aperture was small. On both sides of the face there were two distinct, symmetrical areas of fat accumulation. A similar fat deposit was found in the region of the parotid gland and over the horizontal part of the mandible. The subcutaneous fat in other parts of the face was rather poorly developed. The skin over his lower legs and feet showed the most characteristic changes. Starting downward from the knees the skin appeared taut and tightly stretched over the underlying structures and over the ankles and insteps became so

tightly adherent to the underlying tissue that the motion in the ankle joints and phalangeal joints was grossly impaired. Large *ulcers*, the size of a silver dollar, were present over both Achilles tendons. Several smaller ulcers were found over the malleoli, the lateral surfaces of the feet and between the large and second toes. The ulcers seemed to be located on parts exposed to pressure. The patient himself reported that the ulcers appeared first at the age of 24 and healed very slowly or not at all, draining a thick fluid. Most of the ulcers were covered with a thick, greenish, fibrinous membrane. The ulcers had been painful, especially at night, to



FIG 11 Sidney O The small, thin upper arms and lower legs in direct contrast to globulous abdomen

such a degree that morphine had to be given. Besides the active ulcers there were many scars from healed ulcerations. Both large ulcers over the Achilles tendon were grafted by Dr E Cooney, the grafts healed\*. Slight linear pigmentation of a light brownish color together with some scaling along the pigmented lines was noted. There were no telangiectases. The skin over the phalanges had a reddish hue, whereas the color on all other areas involved was whitish and waxy. There was no pitting on pressure. The skin on the lower parts of the arms and hands was also taut, but not so tightly stretched over the underlying tissue as on the lower legs and feet. On the dorsal surface of the hands the thin, atrophic skin was even pliable, like tissue paper, whereas over both wrists the skin was tightly drawn. The circum-

\* After six months a new ulcer started on the edge of the graft

ference of the wrist was 14 cm , of the upper arms 20 cm , of the calf 24 cm , and of the ankles 16 cm In these parts of the body the *subcutaneous fat tissue* was extremely scanty One got the impression that this lack of subcutaneous fat paralleled the atrophy and tightness of the skin The *muscles* of the distal parts of the ex-



FIG 12 Sidney O Taut skin tightly stretched over underlying tissue, motion impaired in both ankle joints, hallux valgus Ulcers on left inner malleolus, on lateral sides of feet.



FIG 13 Large ulcers on Achilles tendons

trémities were thin and poorly developed, but there was no restriction of motion due to paresis or paralysis of the muscles Where there was restriction of motion it was the result of the tightly stretched skin Both feet were extremely flat and everted with hallux valgus formation The phalangeal *joints* of the hands and feet showed



thickening of the periarticular tissue as seen in arthritis. All the toes were small and immobile. The *toe-nails* were present but atrophic. The finger-nails were short. The patient reported that they grew very slowly. The arms and legs, as a whole, appeared extremely thin and gracile. The small hands and feet, lacking any fat tissue, in contrast to a rather round abdomen, gave the extremities a grotesque appearance. Roentgenograms of the bones, especially of the arms where the dermatosis is evident, showed severe *osteoporosis*. In the same roentgenograms the arteries of the lower legs and feet showed calcification due to arteriosclerosis. The arterial pulse could not be felt in either dorsalis pedis artery. Arteriosclerosis, but to a lesser degree, also involved the arteries of the upper arm. *Eyes* (Note of Dr J J Skirball) "Cataract extraction, left eye, 1936, eight years ago. Right eye, 1939, five years



FIG 14 Healed ulcers of Achilles tendons after grafting

ago. Some capsular remnants. Patient has had a secondary iridotomy. Fundus Disk is of good color, the margin is clear, no elevation of the disk is seen. The arteries are moderately narrowed and slightly angulated, also veins are slightly narrowed. The changes on the arteries indicate early arteriosclerosis. There is definite proptosis of both eyes, no lid lag." The nose was small and beak-shaped, the nostrils were freely movable. The *chin* was small but not retracted. The ears were small, but flat and protruding laterally from the head. The drums were very thin and almost atrophic. Hearing was good in both ears. *Voice* was high pitched. *Laryngoscopic findings* did not show any abnormal change. *Teeth* had all developed and were in fairly good condition. The *chest* was of normal diameter. The *lungs* were normal. The *heart* was normal in size, no murmurs were heard. Blood pressure was 125 mm Hg systolic and 85 mm diastolic. *Endocrine features*. The short stature, the general senile appearance and canities have already been mentioned. The thyroid was not enlarged. The proptosis of the eyes was not a true exophthalmos. There was no lid lag. There were no features of hyperthyroidism. Basal metabolic rate was -15. Total cholesterol was 172 mg per cent, free cholesterol 39.5 mg per cent, ester cholesterol 132.5 mg per cent. The penis was very small in size. The two testes were descended but were of small size. The prostate was small. His sexual desire was not very strong. He sometimes had ejaculations. He was not married. Follicular stimulating hormone in blood was reported negative, 3.24 mg

of 17 ketosteroids per 24 hours were excreted. Creatine was 0.8–0.61 mg per cent in 24 hour urine. Sugar was present in traces. Sugar tolerance curve: fasting 150 mg per cent, one-half hour 274 mg per cent, one hour 286 mg per cent, two hours 278 mg per cent, three hours 272 mg per cent. Calcium was 11.8 mg per cent, phosphorus, 3.6 mg per cent, alkaline phosphatase, 22 Bodansky units. Other laboratory findings: Total serum protein was 8 gm per 100 cc, albumin, 5.5 gm, globulin 3.2 gm. Blood sedimentation rate was 28 mm in 20 minutes, 74 mm in one hour (Blood sedimentation rate was increased, probably owing to ulcers of the leg). Wassermann and Hinton reactions were negative. Hemoglobin was 75 per cent, red blood cell count 2.24 million per cc, color index 0.9. Leukocytes were 10,000 per mm. Differential count: Band forms 5 per cent, adult neutrophils 63 per cent, eosinophils 3 per cent, basophils 1 per cent, lymphocytes 16 per cent, monocytes 12 per cent. Platelets were normal. The appetite of the patient was excellent. In the hospital he consumed a diet of 2500 to 3000 calories without gaining weight.

*Case 2* *Nathan O*, 34 years old, had the same schooling as his brother *Sidney*. He also graduated from a pharmaceutical school in Providence and practiced thereafter with his brother, as a pharmacist in his own drug store. He was intelligent, also, but had less literary ambition than his brother. As a boy, until he was 16, his maximum weight was 140 pounds. At the age of 20 he lost considerable weight. This weight loss was believed to be due to hyperthyroidism. The patient was told that he had an internal goiter, but only a slight external one. A subtotal thyroidectomy was done when he was 21. After the operation he lost further weight. It was then discovered he had diabetes. He was put on insulin and his diet was regulated. He controlled his treatment himself and the urine was sugar free for years. In July 1943 his left foot became infected and gangrene of the second and third digits developed. It was thought that this infection was due to a diabetic gangrene, but apparently the infection and gangrene developed from an infected ulcer. An amputation below the left knee was performed by Dr L. S. McKittrick. The pathological report (Dr B. Castleman) was "Advanced arteriosclerosis, thrombosis and recanalization. Gangrene with fistula formation." After the patient came under our observation Dr McKittrick sent us the following note: "His whole appearance is unusual. His skin is inelastic, almost that of a patient with scleroderma. He did not do as well after his amputation as most patients do in that there was a small area that necrosed." He was put on an 1800 calorie diet with 25 units protamine zinc and 10 units regular insulin. Six months later the patient was admitted to our hospital. At this time the 24 hour urine contained 8–10 gm sugar. *Appearance* He was short in stature, five feet and three-quarters inches (144 cm), weight 93.5 pounds. His likeness to his brother was surprising. Many people considered the brothers twins. His face, however, was not as full as his brother's. The fat pads over the parotid and on the lower mandibular region, as seen on *Sidney*, were not present on *Nathan's* face. He looked much older than his actual age. The general impression was that he appeared even more senile than his brother. The scalp hairs began to turn gray at the age of 16. They were now the same indefinite grayish color as seen on his brother. They were also fine in texture but very scarce. The hair of his face was more abundant than that on his brother's face. He had to shave almost every other day. Also, the hair on chest and abdomen was better developed. The distal parts of both extremities were hairless. The pubic hairs were poorly developed, not curled, but straight and short. The patient noticed the first changes in his skin at the age of 20. "Corns," i.e., circumscribed areas of *hyperkeratosis*, developed on both heels, on the lateral parts of his feet and under the large toes. The hyperkeratotic areas were prominent over the skin and had a shell-like configuration consisting of horny layers. *Skin ulcers* appeared on the points of pressure on the malleoli, on the lateral parts of his feet and on the left instep and over the left second

and third toes. Apparently a secondary infection developed in 1943 from the ulcers of the toes which resulted in an amputation below the knee of the left leg. At present a large ulcer, the size of a quarter, was present on the inner side of his right foot, causing excruciating pain, usually during the night. Opiates were necessary every night to relieve this pain. The skin over the Achilles tendon, unlike that of his brother, was not ulcerated. A smaller ulcer developed on the skin of the right second digit where it pressed against the skin of the large toe. The skin of his face was taut but wrinkled. Long, stiff, nasolabial folds gave his face an old appearance. The



FIG 15 Nathan O. Amputated left leg. Taut skin tightly stretched over the right lower leg. Ulcer on the inner side of the foot.

aperture of his mouth was small. The skin over the stump of his left leg was normal on the thigh but around the knee, just over the amputation, the skin was atrophic. The pressure of the prosthesis had caused reddening of the skin. (Ulcer formation on the lower end of the stump was feared.) The skin over the right lower leg showed the same characteristics as his brother's. The skin from the knee down was taut, atrophic, and stretched over the ankle and metatarsal joints. Scaling and slight linear pigmentation were visible. Motion of the right foot was limited because of the tightness of the skin. He was able to walk with the help of two sticks, when the prosthesis was in place. The *subcutaneous fat tissue* and the *muscles* of the right leg from the knee down were extremely poor. Circumference of the right ankle was 18 cm. Circumference of the left calf was 23 cm. The skin on both upper arms and hands was taut, but not so tightly pulled over the wrist that it could not be wrinkled.

The texture of the skin was thin and atrophic. The subcutaneous fat was almost lacking on both upper arms and the muscles were very thin. Circumference of the wrists was 12.5 cm. Circumference of the upper arms was 20 cm. The *joints* had the same appearance as presented by his brother Sidney. Roentgenograms of the osseous system, especially of the extremities, showed *osteoporosis*. The arteries of the right leg were extremely calcified. That those of the left leg were in a similar state was confirmed by the pathological examination after amputation. *Arteriosclerosis* was more advanced than in the case of his brother Sidney. Both cataracts had been extracted. The patient had had a secondary iridotomy. The fundi showed changes characteristic of arteriosclerosis. The *ears* were small and flat, protruding laterally from the head. The inner ears were normal. His nose was somewhat longer than his brother's. The nostrils were freely movable. The *chin* was small and slightly retracted. The *voice* was high pitched and husky. *Laryngoscopic findings* (Dr Kelemann) "Even after anesthesia only two-thirds of the larynx is seen because the large, flat epiglottis covers the other third. The right side of the larynx is normal. At the left side the vocal cord is covered in its central part by a diffuse red structure moving with the vocal cord. This structure may consist of distended veins or may consist of an hemangiomatous structure. The mucosa of the left ventricle is prolapsed. The arytenoid movements are free as are the other movements of the larynx." *Vascular system and heart* As has already been stated, the roentgenograms showed sclerosis of the arteries of the right leg. The examination of the amputated left leg showed, as above stated, severe arteriosclerosis. The heart was of normal size. There were no murmurs. Action was regular. Blood pressure was 160 mm Hg systolic and 90 mm diastolic. Liver and spleen were not enlarged. *Endocrine features* His short stature and presenile appearance have already been described. His thyroid was not palpable, the scar of a partial thyroidectomy was visible. His eyes were protruding but there was no lid lag or other symptoms which would indicate hyperthyroidism. Basal metabolic rate was  $\pm 0$ . The testicles were descended but small. The scrotum was very small, the size of that of a 10 year old boy. The penis was short. (Sexual desire was minimal but ejaculations did occur. He had never had intercourse.) The excretion of total 17 ketosteroids was 5.8 mg per 24 hours. Sella turcica was within normal limits. His fasting blood sugar ranged between 205-251 mg per cent. The patient excreted 8-10 gm of sugar, in spite of receiving 25 units of protamine zinc and 10 units of regular insulin, and a diet of 1,800 calories (170 gm carbohydrates, 85 gm protein, 87 gm fat). Other laboratory findings were 75 per cent hemoglobin, 4.44 million red blood corpuscles per cu mm, color index 0.87, leukocytes 9,800 per cu mm. The differential count was normal. Total serum protein, 8.08 gm per 100 cc, albumin, 5.26 gm, globulin, 2.82 gm. Blood sedimentation rate was 75 mm in one hour. Blood Hinton reaction was negative. Creatine excretion was 1 gm in 24 hours. Blood calcium was 11.8 mg per cent, phosphorus 3.6 mg per cent, alkaline phosphatase 2 Bodansky units.

*Comment* The two brothers not only looked alike but had the following characteristics in common: (1) Shortness of stature, (2) atrophy of the subcutaneous fat tissue and the muscles of the lower arms and lower legs, hands and feet, (3) small hands and feet, (4) canities (premature graying of scalp hair); (5) scarce scalp hairs, (6) atrophic dermatosis of lower legs, feet, upper arms and hands, partially on face, (7) pressure ulcers on exposed parts of the feet, (8) circumscribed areas of hyperkeratosis on feet and insteps, (9) arteriosclerosis of the arteries of the extremities, (10) osteoporosis, (11) diabetes or potential diabetes, (12) hypogonadism and reduced sexual desire. The description of other cases in the literature is so

similar in most of the detailed features that there is no doubt that this syndrome first described by O Werner is a clinical entity. It is evident from the family trees, especially from that published by E Krebs, E Hartmann and F Thiebaut<sup>14</sup> (see page 565) that this syndrome may, also, occur as an incomplete form, so called "forme fruste".

The study of the cases of brothers S O and N O, however, leads us to doubt whether or not one of the outstanding symptoms of Werner's syndrome is correctly described by the term "scleroderma" or "poikiloscleroderma". To the best of our knowledge there is no case of true scleroderma described in the literature in which this disease occurs in families as a recessive familial disorder. Diffuse scleroderma usually involves the skin and tissue beneath the lower eyelid, the skin covering the nose and nostrils and the skin around the mouth and the chin. In most of these cases the skin of the neck, of the thorax and of the abdomen as well as the skin of the extremities is involved. In many cases of true scleroderma an intensive melanotic pigmentation is seen in some areas of the body, especially on the neck, in the axilla, on the trunk and buttocks. Areas of circumscribed hyperkeratosis, however, occurring on feet, insteps and elbows are not a feature of true scleroderma. In Werner's syndrome, in contrast to scleroderma, the skin changes begin with circumscribed areas of hyperkeratosis beneath the heels, beneath the large toes, on the lateral parts of the feet as well as on the instep and over the Achilles tendon. In Werner's syndrome areas of melanotic pigmentation are never observed. Scaling, however, along very fine, faintly yellowish brown stripes may be found in some cases. As a whole the skin in Werner's syndrome is white and waxy in color and has a reddish hue only on the parts of the extremities where it is exposed to pressure from clothes and shoes. These distinct differences in clinical features of true scleroderma and the "pseudo" scleroderma in Werner's syndrome are strikingly supported by the histological examination of the skin biopsies obtained from both brothers O. The histology of true scleroderma is characterized by edema, homogenization, fibrosis and sclerosis of the collagen fibers and obliterative changes in the vessels of the cutis. Lymphocytic infiltration of the subcutaneous tissue especially about the blood vessels is a characteristic histologic feature. These characteristics of true scleroderma are not found in the biopsies of our cases. In the histological examination of the skin biopsy of Sidney O the horny layer seemed to be of normal thickness and structure. The pars papillaris was either somewhat flattened or definitely flattened. There was no homogenization or sclerosis of the connective tissue underlying the papillae nor homogenization of connective tissue of the pars reticularis. The hair follicles and the sweat glands were not numerous and, if present, were not well developed. No proliferative nor necrotizing arteritis was visible in the arteries of the subcutaneous tissue. The subcutaneous veins were more distended than usual. The elastic fibers of the corium were loose and appeared essentially unaltered. Fat cells were almost absent in the subcutaneous tissue.



Fig. 16 Skin biopsy of Sidney O Papillae fairly well preserved, subcutaneous tissue normal, no proliferative necrotizing arteritis visible

We are indebted to Dr H Montgomery, of the Mayo Clinic, Section on Dermatology, for examination of our slides of S O. He was kind enough to give the following opinion: "I would guess that the biopsy and slides of Sidney O (N 6018) were taken from the leg, probably the lower part of the leg, because of the large varicose veins present in the subcutaneous tissue. Some atrophy of the hair follicles is present, but this often occurs in skin taken from the legs and areas where the skin has been subject to friction, as from socks and garters. There is no evidence of so called senile skin, such as tinctorial changes in the staining of the collagen or basophilic staining of the elastic tissue, which can be seen in polychrome methylene-blue and hematoxylin-eosin stained sections. The slides of the skin show practically no inflammatory reaction, no appreciable obliterative changes in any of the vessels. The connective tissue fibers appear essentially normal and there is no decrease in thickness of the cutis. All this speaks against scleroderma.

"Pseudosclerodermatous infiltrations with ulceration, especially in the vicinity of the ankles, and poikiloderma-like changes are often seen in the relatively rare skin condition known as 'acrodermatitis chronica atrophicans'. Clinically, however, there usually is no systemic disturbance or evidence of systemic disease, and, histopathologically there is a rather specific picture with marked atrophy of the epidermis and flattening of the rete ridges with partial to almost complete loss of the cutis, the cutis being replaced by a dense infiltrate that is separated from the epidermis by a normal 'grenz' or border zone. Unless the sections were taken from a pseudosclerodermatous area one can rule out acrodermatitis chronica atrophicans on the basis of these sections."

The skin biopsy taken from Nathan O showed more flattening of the pars papillaris than that of his brother Sidney. The histological pattern, however, was the same as described in the slides of Sidney O. Here, also, the connective tissue of the pars reticularis was not homogenized or sclerosed. There was no inflammatory reaction in the rete. A few lymphocytes were occasionally found around some blood vessels. In sections stained for elastic tissue no abnormal conditions were found either in the case of Sidney or Nathan O. The *muscle biopsies* taken from Sidney O and Nathan O showed no cellular infiltration or specific changes.

It is evident from these histological findings that the skin changes in Werner's syndrome are not identical with the skin changes found in diffuse or localized scleroderma. Such a classification of the skin disorder in Werner's syndrome is not justified since neither the clinical picture nor histological examination coincides with scleroderma or poikiloscleroderma. It seems more appropriate to designate the skin lesions in Werner's syndrome by a simple descriptive name such as "heredofamilial atrophic dermatosis with skin ulcers."



FIG 17 Skin biopsy of Nathan O. Papillae are definitely flattened, subcutaneous tissue not homogenized, some veins distended. No inflammatory infiltration of arteries or tissues





FIG 18 Higher magnification of figure 17

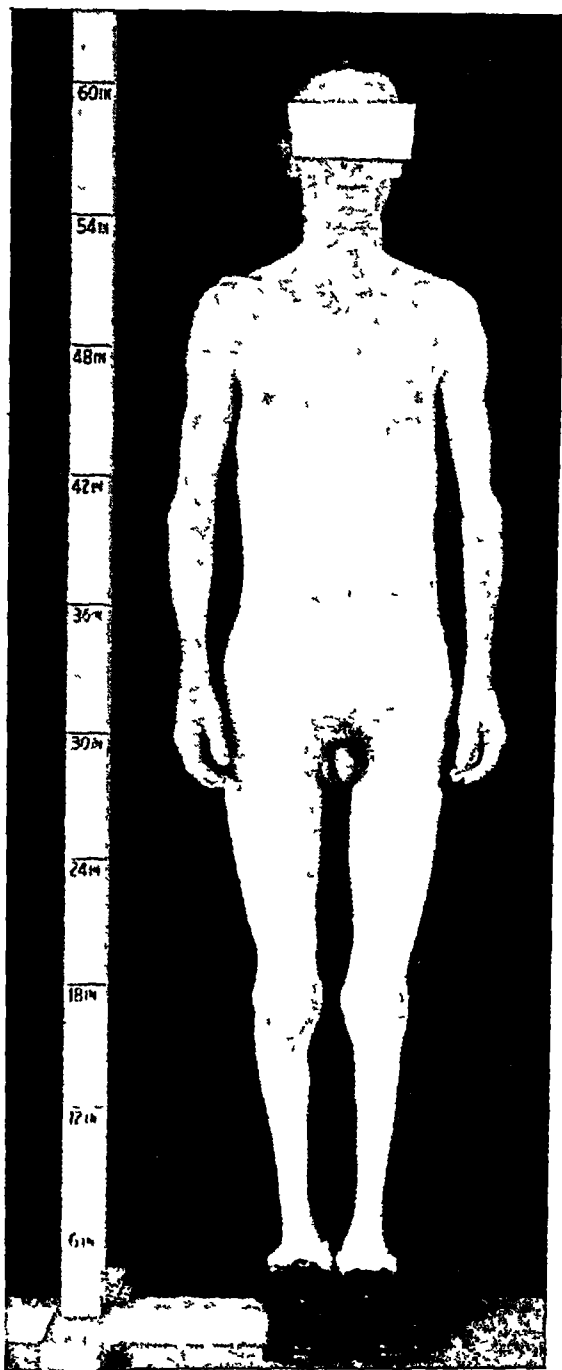


FIG 19 George St. General leanness, extremely thin legs and arms

*Case 3* George W St, 39 years old, was studied on the Medical Service of the Massachusetts General Hospital\* Mother and father were direct cousins Both

\* Dr Fuller Albright was invited to see Sidney O in our hospital in consultation He remembered at once that he had observed a similar case. I am very much indebted to him for letting me examine this patient, George St., and include his case history in this paper

were normal. He had two married sisters, 46 years old and 40 years old. The older sister had two healthy boys in the Navy. The younger sister had a healthy girl, 17 years of age. The patient was born a normal child but was delicate. He graduated from high school and from a school of architectural drafting. *Appearance* He was short in stature—five feet. He had grown very little since the age of nine. Weight was 75 pounds. His maximum weight was 100 pounds, at the age of 22, when he entered the Navy, but at the time of his discharge he weighed 85 pounds. He looked older than his actual age. He did not know when his hair started to turn gray. At

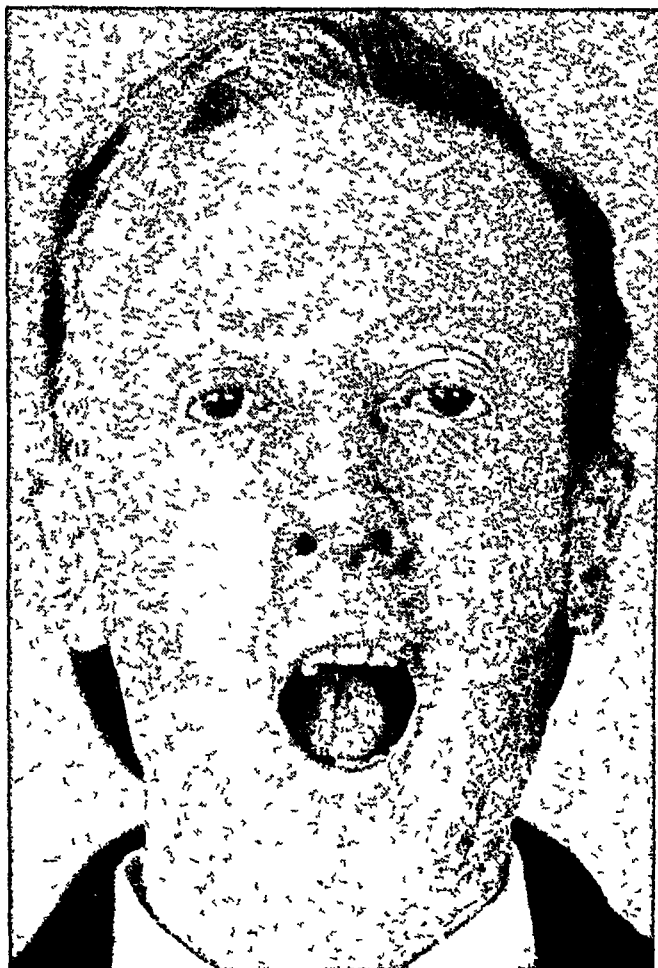


FIG 20 Skin under lower eyelids wrinkled (in contrast to scleroderma). Aperture of mouth small. Hairs are fine and gray. Presenile appearance.

the age of 33 he was completely gray. The scalp hairs were now scarce, fine, and of an indefinite grayish color. His eyebrows were normal. He had only a few eyelashes. He shaved about twice a week. His beard was gray. His body hairs were almost absent. His pubic hairs were scarce and straight, not curled. The skin of his face was taut, but movable over the underlying structures. The nasolabial folds were distinct and formed taut, longitudinal lines. The aperture of his mouth was small but the opening of the mouth was not hampered. The skin of his neck and thorax was thin, transparent and movable. The skin of his upper arms and lower legs was taut and tightly stretched over the underlying tissue. The skin above the knees and elbows was normal. Although the skin on the dorsal parts of his hands was pliable, the skin over both ankles and both feet was so tightly pulled over the

bones that motion of both ankle, metatarsophalangeal, and phalangeal joints was limited. He walked with stiff ankle joints and everted feet.

*Skin biopsy* "There is slight superficial keratosis. The rete pegs have disappeared. The pars papillaris is flat. The zone of prickle cells is reduced. No inflammatory changes of the subcutaneous tissue are seen. There is no cellular infiltration around or within the arteries. The walls of the arterioles are somewhat thickened. The subcutaneous tissue is loose. Neither homogenization nor sclerosis of the subcutaneous tissue is seen. The subcutaneous fat is very scarce. Some veins of the subcutaneous tissue are distended. The elastic fibers are essentially unaltered.



FIG 21 Skin over both ankles tightly pulled, motion in ankle-joints impaired. Ulcers on left malleolus and sides of feet. Areas of hyperkeratosis.

Hairs and sebaceous glands are almost absent in this section." Areas of *hyperkeratosis* on his feet were the first signs of skin changes the patient had noticed. He reported that at the age of 17 he became aware of calluses on both soles under the large toes and both heels. No ulcers were present at this time. The first *ulcers* developed at the age of 37 on the lateral parts of both feet. He now had circumscribed areas of hyperkeratosis under both large toes, under both heels, and on the lateral margins of his feet. The ulcers were almost healed but the scars of former ulcers were visible on both feet. The *subcutaneous fat tissue*, as well as the *muscles* of upper arms, hands, lower legs and feet, were underdeveloped. The lower parts of arms and legs were so thin that they had a skeleton-like appearance. Circumference above the wrists was 13 cm, above the ankle joints it was 15 cm. Hands and feet were very small in size. The fingers seemed somewhat deformed because the interphalan-

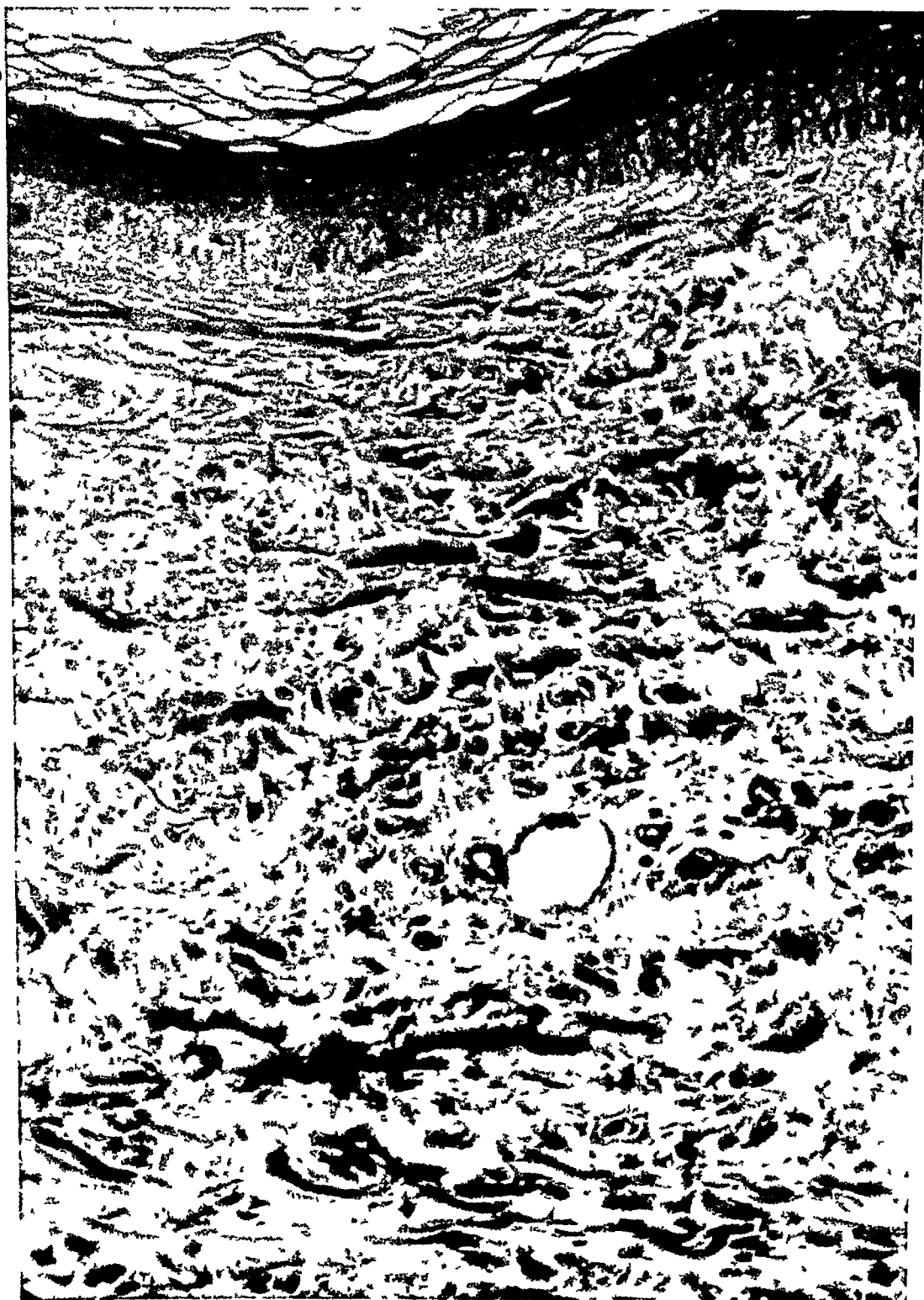


FIG 22 Skin biopsy of George St. Papillae are entirely flattened. Small mucous layer. Prickle-cells reduced in number. Subcutaneous tissue normal, not homogenized. No inflammatory infiltration around arteries or in subcutaneous tissues. Some distended veins.



FIG 23 Higher magnification of figure 22

geal *joints* were prominent, as in an arthritic person. The roentgenograms of the bones in the parts where the dermatosis of the skin was evident showed *osteoporosis* due to decalcification. In the roentgenograms, made at the Massachusetts General Hospital, November 30, 1941, small areas of calcium deposits were seen in the soft tissue close to the right fifth metacarpal phalangeal joint and of the proximal phalanx of the fourth right finger. Similar areas of calcium deposits were also seen around both ankles. At present calcification was noted only in the Achilles tendon. Calcification of the arteries was not visible in the roentgenograms of both lower legs. *Eyes* At the age of 30 *cataracts* developed in both lenses. The cataracts were successfully extracted at the age of 34 by Dr. Chandler of the Massachusetts General Hospital. Both eyes were now aphacic and showed scars of a healed iridocyclitis. There was no proptosis of the eyes. The *nose* was fine in contour and somewhat elongated. The *chin* was small but not retracted. The *ears* were small and flat but did not protrude laterally from the head. The *voice* was high pitched and hoarse. The *teeth* were all developed but carious. The roentgenogram of the *lungs* showed thickening of the apical pleura on the right side. *Vascular system* The heart was normal. Blood pressure was 130 mm Hg systolic and 80 mm diastolic. There was no visible arteriosclerosis. Electrocardiogram was normal. The reflexes were normal. A myotonic reaction could not be elicited. *Endocrine features* The shortness of stature and the senile appearance with graying of the scalp hairs has already been discussed. The thyroid was not palpated. Basal metabolic rate in 1941 was  $-14$ , in 1943,  $-32$ . The sexual organs were very small. The penis was short. The scrotum was small in size. The testes, although descended, were of the size of those of a 12 year old boy. In 1941 the 17-ketosteroids in the 24 hour urine were 13.3 mg, in 1943, 5.7 mg. The sella turcica, on roentgen-ray examination was normal. *Laboratory findings* Total serum protein, sodium and potassium and calcium determination in the serum were normal.

*Comment* This patient was the child of first cousins, but as far as could be ascertained there was no similar case in his ancestry. The features of Werner's syndrome present in George St. were Presenile appearance, shortness of stature, canities, skin changes consisting of stretching of the taut skin over the underlying structures on the lower legs and feet, skin ulcers, areas of hyperkeratosis, atrophy of subcutaneous tissue as well as muscles of the upper arms and lower legs, hands and feet, small chin, hands and feet, osteoporosis, sexual underdevelopment. Although potential diabetes and arteriosclerosis were not evident in this case the other features are convincing that this case belongs to the group of Werner's syndrome. In 1941 our patient underwent a lumbar sympathectomy because it was thought that the skin changes were due to scleroderma and the ulcers were due to trophic disturbances of the skin. A follow-up note of the Massachusetts General Hospital, in the case history, reads as follows: "I cannot see that any benefit was obtained from this operation. Since that time his condition has remained essentially unchanged." It seems, therefore, that the ulcers are not the result of a trophic disorder. The good healing of the ulcers after grafting, in the case of Sidney O., supports the opinion that the ulcers are due to the vulnerability of the atrophic and stretched skin to outside pressure from shoes and clothes. The gross skin changes are the same as in all cases reported. The histological examination of the skin biopsy concurred with the biopsies of the

brothers Sidney and Nathan O in that the characteristics of true scleroderma were not found Homogenization and sclerosis of the subcutaneous tissue as well as inflammatory reactions consisting of lymphocytic infiltration in the subcutaneous tissue and proliferative arteritis were absent These negative findings on three patients with Werner's syndrome demonstrate that the taut and stretched skin is not the result of true scleroderma but rather a part of the general abiotrophic process which involved the endocrine glands as well as the whole body It is highly suggestive that such an abiotrophic degenerative process which manifests itself in the second and third decades of life may originate in a recessively transmitted hereditary defect of the germ plasm

*Case 4 Miss M F, 29 years old* There was no history of intermarriage in her ancestry No similar cases were known in the family The family was highly intellectual Father and brother were outstanding professors in medical schools in Germany A maternal uncle was one of the great physiologists of the past century The girl was mentally retarded, having the mentality of a 12 year old child She graduated, however, from a private school Her appetite became very poor at the age of 17 Instead of eating her meals she hid her food and threw it away when she was unobserved *Appearance* She was very short in stature and considerably underweight She looked like an old woman, about 20 years older than her actual age The scalp hairs began to turn gray around the age of 20 They were sparse, fine and of an indefinite grayish color The eyebrows as well as the eyelashes were scarce The axillary hairs were completely absent Only a few short pubic hairs were found The skin of the face was wrinkled, but taut Longitudinal firm nasolabial fat gave the face an old appearance The skin on the chest and abdomen was thin and atrophic No pigmentation or telangiectases were present The skin of the upper arms and hands was atrophic and thin Over both hands the skin was pliable like tissue paper In contrast to the skin on the forearms and hands the skin over both lower legs was taut and adherent to the underlying structures, the latter especially noticeable over the ankles and the insteps The motion in the ankle joints was moderately impaired by the stretched skin, and she walked with everted feet She complained of pain in circumscribed areas of *hyperkeratosis* under both large toes, both heels and on the external sides of the feet She reported that she had *ulcers* on the lateral malleolus and on the instep from pressure of her shoes The ulcers healed only after a long time Ulcer scars, but not active skin ulcers, were visible *Nails* on hands and feet were poorly developed, but all were present The subcutaneous fat tissue and the muscles on both lower legs and upper arms were thin and poorly developed The lower legs had a skeleton-like appearance Roentgenograms of the bones were not made The phalangeal joints on both hands had the appearance of arthritic joints with thickened periarticular tissue The patient did not complain of pain in her joints At the age of 24 she noticed difficulty in reading Beginning *cataracts* were found At the time she was observed, at 29, the cataracts had almost matured Her *nose* and *chin* were small The *ears* were small and flat, but did not protrude laterally from the head The *voice* was high pitched and slightly hoarse The *lungs* were normal The *heart* was normal in size Blood pressure was 130 mm Hg systolic and 90 mm diastolic There was no note in regard to the arteries *Endocrine features* Senile appearance, canities, and the very short stature have already been described The thyroid was not enlarged No proptosis of the eyes was noticed Basal metabolic rate was not recorded The patient first menstruated at the age of 16 After that menstruation was sparse, occurring only a few times during the year



and ceased at the age of 25. Gynecological examination reported by a gynecologist (Dr. Weber): "External genitalia normal; hymen intact. By rectal examination neither uterus nor ovaries could be felt distinctly; probably underdeveloped." No records of laboratory examinations were available.

*Comment.* The patient was seen almost every year, from the age of 29 to 37. The cataracts were operated upon at the age of 31. At the time she was under observation I did not make the diagnosis of Werner's syndrome because I was then not aware that such a syndrome had been described. Since in later years I have become familiar with the literature there is no doubt that the features of this patient, i.e., short stature, canities, cataracts, atrophic dermatosis with taut and stretched skin, sexual underdevelopment, justify in retrospect the diagnosis of Werner's syndrome. Stunted growth resulting in short stature and sexual underdevelopment was reported by R. F. Varney, A. T. Kenyon and F. S. Koch<sup>17</sup> and by F. Albright, P. H. Smith and R. Fraser<sup>18</sup>. L. Wilkins and W. Fleischmann<sup>19</sup> designated this syndrome as "ovarian agenesis" because they demonstrated in their cases, by their histological studies, that the ovaries did not develop. Wilkins and Fleischmann suggest that ovarian agenesis as well as stunted growth is due to defects of the germ plasma and not to endocrine deficiencies of normally developed organs. "It is well recognized that multiple germinal defects frequently occur in the same individual." We are inclined to explain Werner's syndrome as the result of multiple germinal defects because it presents recessive characteristics and is of heredofamilial occurrence and because its endocrine manifestations, namely stunted growth and sexual underdevelopment, are only a part of its multiple features. Wilkins and Fleischmann tabulate 32 cases published by different authors in which they suggest the presence of ovarian agenesis. Only one of these cases (case 10 by F. Albright, P. H. Smith, R. Fraser<sup>18</sup>) exhibited progeria and cataracts in addition to ovarian agenesis. Although skin changes and heredity are not reported, it seems possible that this case is related to the group of Werner's syndrome. When in the future we have better learned how to differentiate the features of functional endocrine deficiencies from the endocrine features resulting from germinal defects, reports of Werner's syndrome and related syndromes will become more numerous.

## II ROTHMUND'S SYNDROME

*August Rothmund*,<sup>20</sup> in a paper entitled "Cataracts in Association with a Peculiar Degeneration of the Skin" in the *Archives der Ophthalmologie*, 1868, writes as follows: "A boy five years of age was brought to the ophthalmological clinic in Munich who suffered from a cataract of one eye which was not due to a trauma, and gradually developed during a couple of weeks. I noticed there was already at this time a peculiar marmorization of the skin of this boy. To my surprise two other children living in the same vicinity and also suffering from cataract and peculiar skin

degenerations came into the clinic. My attention was even more attracted by the report of the parents of the children claiming that several such blind children exhibiting the same skin changes were living in the same section of the country. Experienced dermatologists (colleagues of the medical faculty of the University of Munich) to whom I demonstrated the cases, assured me that they never had seen a similar skin disorder. For this reason I decided to explore the situation in loco and to visit the 'Kleine Walsertal' during the fall vacation. The 'Kleine Walsertal' in the Austrian Bregenzerwald in Vorarlberg, is a small dead-end valley surrounded by high mountains of the Alps, which could be reached only by a small pass road from the Bavarian Allgau mountains. In this valley are located only three little villages, Ritzlern, Hirscheck and Mittelberg with altogether 1500 inhabitants. Almost all the families of this valley are related, and intermarriage in the same family is not infrequent. Rothmund found in each of these three villages one family, the children of whom exhibited cataracts resulting in blindness and simultaneously occurring skin alterations.

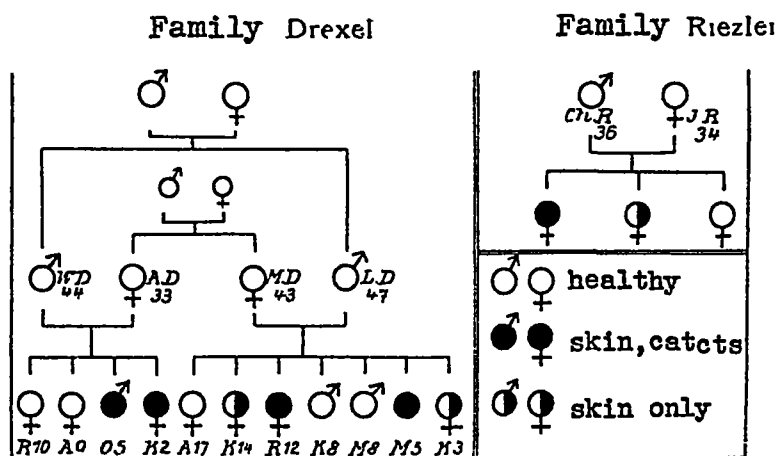


FIG 24 Family tree of the Drexels and Riezlers

The three families involved were (1) Family Wolfgang Drexel in Mittelberg. There were four children. The two older ones (10 and seven years old) both females, were normal. The two younger ones, a boy, Oswald, five years old, and a girl, Katherine, two years old, it was noted, had skin changes at the age of six months and cataracts at the age of five. (2) Family Lukas Drexel in Hirscheck. There were seven children. The oldest, a female of 17, was normal, the second, a female, Karolina, 14, had slight skin changes but no cataracts, the third, a female, Rosamunde, 12, exhibited skin changes at three months and developed cataracts at six. The fourth and fifth were male twins, eight years old, and normal. The sixth, a female, Maria Katharina, five years old, developed skin changes at the age of three months and cataracts at the age of four. The seventh, a female, Maria Karethina, three years old, also developed skin changes at the age of three months, but the eyes were still normal. (3) Family Riezler, in Ritzlern, had three female children. The oldest, Rosamunde, four years old, developed skin changes within three months of birth, and beginning cataracts at the age of four years. The second child, Therese, three years old, developed skin changes within three months of birth. Beginning cataracts were

found at the age of three years. The third child, also a female, five years old, did not then show signs of skin abnormalities or cataracts.

Only one *grandmother* of one of these families had a similar skin anomaly, but was not blind. No other ancestor was afflicted with a similar abnormality. Rothmund reported that all these children were similar in their *general appearance*. The children were physically and mentally normal in development. Other than the eyes and skin all organs were found normal. Urine contained no sugar or other abnormal



FIG 25 Rosamunde R (Reproduced from paper by Rothmund) Telangiectases, corresponding to livedo reticularis, surround scaling white skin

constituent. The *cataracts* formed from the age of four to six. They developed rapidly in both eyes, never unilaterally. The cataracts started as star-like opacities at the lower posterior pole of the lens and extended, in a short time, toward the center of the lens, resulting in blindness. The *skin changes* were not present at birth. Marmorization of the skin became visible first in the face, three months after birth. Later the skin on the knees, on the ears, on the buttocks and on the extremities—first the extensor, later the flexor surfaces—became involved. Only the vola manus and the bends of the elbows and knees remained free. In the first stages the skin

changes corresponded to the livedo reticularis, later striae and round reddish spots appeared. The striae were not prominent over the surface of the skin but were more or less beneath the surface. With the naked eye the surface of the skin looked level and no prominences were visible. Applying pressure with the finger upon the skin the reddish color disappeared but a light yellowish-brown color remained. The reddish color of the lesion after scaling became brown-red and yellowish and finally appeared as a firm colorless scar. The skin then had an areolated appearance resulting from the normal skin being encircled by these yellowish or colorless scars. The process described went on continuously but slowly, with the result that red lines, like telangiectases, and scar tissue were present at the same time. Neither itching, vesiculations, ulcers nor crusts were present. The areas of the skin now involved were extremely fine, soft, white and transparent so that the veins beneath the skin were visible to their smallest ramifications.

The *histological examination* performed in 1868 is inconclusive when compared with present-day methods. Staining methods with aniline dyes had not been developed. A piece of superficially unaltered skin and a piece corresponding to one of the reddish striae were examined. The normal skin of the patient showed the same picture as normal skin does, but in the corium layer the number of elastic fibers seemed less than in a normal skin. The horny layer of the pathologically changed piece of the skin was not undulated but flat and not transparent. The mucous layer showed the same condition, but the changes were more marked in the center of the red striae and less in its periphery. The mucous layer was not well defined towards the reticular part of the corium and rested plainly upon it. The pars papillaris was lacking and was replaced by a layer that showed no definite structure. It contained some blood vessels and clumps of hemoglobin derivatives. In separating the mucous layer from the underlying tissue neither indentations nor elevations resulted. Fat droplets were visible between the two layers. The transition of the layer replacing the pars papillaris into the subcutaneous tissue was not clearly defined. The subcutaneous tissue did not show remarkable changes. It was composed of fat droplets, perhaps of fewer hair follicles than normal, some of them not containing hairs, of some coil glands and connective tissue. The elastic fibers were not compressed. Rather loose fascicles surrounded alveolar spaces filled with tissue of the same undefined nature as the one replacing the pars papillaris. Rothmund summarized the results of his examination as follows: "The essential finding of the examination of the diseased piece of skin was the fatty degeneration of the rete Malpighii and the disappearance of the pars papillaris." Concerning the etiology of the disease Rothmund suggests a heredofamilial disorder of the ectodermal layer as the lens is also derived from a bulge of the ectoderm.

*Comment* Designating these skin changes according to the nomenclature of the time as "Parenchymatous inflammation" Rothmund hesitated to give the syndrome a special name since he could not find a description of a similar skin alteration combined with simultaneous formation of cataracts. Skin changes similarly observed in adults were later described in the dermatological literature as "Atrophia Maculosa et Striata." According to Ormsby and Montgomerie<sup>21</sup> such lesions are also observed as a congenital atrophy. These authors believed that the skin changes in the congenital cases are a congenital defect rather than an acquired atrophy. The case of Riehl and Vorner<sup>22</sup> (1903) may be due to a congenital defect and belong to this group. The skin lesions of the children observed by Rothmund were certainly not congenital since they appeared three to six months after birth.

The fate of these children was reinvestigated 67 years after Rothmund's original publication by R. Seefelder (1931). The two children of Wolfgang Drexel had died. Oswald D died at the age of 56 and Maria Katharine D at 40. Oswald had married but had no children. Maria Katharina remained single. Photographs taken of Oswald at the age of 40 showed no skin changes. The scalp hair was ample and apparently not gray, but the face was without mustache or hairs. There were no remarks concerning the height or other physical characteristics which may have developed in later years. The investigation concerning the family of Lucas Drexel was more successful. Katolina, in whom only skin changes were noted, was living at the age of 83. She had 13 children. Only one daughter had her eyes operated upon at the age of 48. Four children died as infants, nine children were alive and healthy. The skin on both arms of this 83 year old woman was thin, resembling tissue paper. Round areas of dark brown pigmentation were observed on both arms. The scalp hairs, even at that age, were relatively well preserved. Her sister, Rosamunde, who had cataracts and skin changes as an infant, was living and aged 76. No report concerning her skin and hair was made. She had not married. The third sister, Maria Katharina, died at the age of 70. She had married but had no children. Maria Karethina, the fourth sister, was alive at the age of 72. Her height was 150 cm (four feet). Her hands and feet were very small and her fingers and toes were short. The size of the hands was that of a 10 year old child. The extremities were very short. The skin over face and forehead showed a network of dark wine-red striae. The skin between the reddish network was yellowish. The skin on the extremities showed no red striae but was thin, like tissue paper, and diffusely pigmented with round areas of darker brownish pigmentation. The scalp hairs had almost completely disappeared at the age of 40. It was especially remarkable that the old woman was mentally very alert, talkative and full of humor.

Concerning the fate of the children of the third family, that of Peter Riezler, no details are known. Seefelder, however, added a report of another member of the family Riezler, who was the product of the intercourse of father and daughter. Peter Riezler, 30 years old, had red striae on his face, round pigmented spots on both arms and hands. He had cataracts in both eyes. His height was 146 cm (below four feet). His mental development was retarded.

The follow-up study of the three families demonstrated that the children originally described lived to an average age or even to an old age. The patients who exhibited cataracts as children, as well as skin changes, did not marry and had no children. Only Rosamunde, who had only slight skin changes, but no cataracts, had 13 children. The other brother and sisters who did not develop cataracts or skin changes, if married, had healthy children. Only one of the original children reported by Rothmund (Maria Karethina Drexel) remained short in stature, had short extremities, small hands and feet and became gray and bald at the age of 40.

A *Nieden*<sup>23</sup> in 1887 described a girl 22 years old who at the age of 15 noticed telangiectases on her face. Small red areas of pea or pin point size developed on the forehead, cheeks and upper part of the neck. Such lesions later appeared as well on the hands and extensor surfaces of the arms. Cataracts formed on the posterior poles of the lenses at the age of 20. Menstruation started late, at 15, and was irregular. "The slim, lymphatic appearance of the girl was striking at the first glance." No other features were reported. Although the occurrence of a similar disease had not been recorded in her family, this case probably belongs to Rothmund's syndrome.

Under the title "*Télangiectasie généralisée et cataracte congénitale*" *F Terrien and Prélat*<sup>24</sup> (1909) reported the case of a six year old girl. Three brothers died during infancy of bronchial pneumonia, complicating measles, no skin changes were present in the case of these infants nor in the case of the parents. It is reported that the child, herself, at the age of three months, already exhibited areas of telangiectasis of the face, the buttocks, and the skin of the extremities, especially on the extensor surfaces. Small areas of brownish net-like pigmentation accompanied the areas of telangiectasis. In addition to these features a thickening of the skin resembling myxedema was noted. The hairs of the scalp were normally developed, however, the eyebrows were very sparse. At the age of six the child had cataracts in both eyes, the first appearance of which was not reported. Although the authors suggested a thyroid deficiency as the cause of the disorder (no data were given concerning the condition of the thyroid), there is no doubt that this case belongs to Rothmund's syndrome. This is evident from the type of the skin lesions as well as from the early development of the cataracts.

*Zinsser*<sup>25</sup> in 1910, described two brothers under the title "*Atrophica cutis reticularis cum pigmentatione*" *V Janovsky*<sup>26</sup> in 1921, under the title "Three cases of familial skin atrophy (*Poikiloderma atrophicum*)" reported three sisters who exhibited skin changes on the cheeks corresponding to the livedo reticularis, with redness in honeycomb configuration, central skin atrophy under scaling and pigmentation. The children reported by Zinsser also had lesions on both hands. These children, however, did not have cataracts. Since formes frustes (incomplete syndromes) were reported in the children of Rothmund's original description (Karolina D had only skin changes but no cataracts) it seems possible that these children, also, are abortive cases of Rothmund's syndrome.

A *Siegrist*<sup>27</sup> in his book "Der graue Altersstar," reported the case of a four and a half year old girl who developed cataracts at the age of six months. The skin changes reproduced from a colored design (figure 19 of the book) were of the same kind as described by Rothmund.

A *F Schnyder*<sup>28</sup> added to the case of A. Siegrist the complete history and description of the case of the younger brother of the patient already reported by A. Siegrist. The child was the youngest of four sisters and brothers. The oldest girl was the patient reported by Siegrist. The two others were healthy. There was no report concerning the intellectual ability of the parents. The boy, five years old, rapidly developed bilateral cataracts. Skin changes had been observed at the age of five months. They developed first on the face as net-like telangiectases, later as pink-reddish striae, which resulted in round areas and stripes of skin atrophy. Pigmented and hyperpigmented areas intermingled with telangiectases were seen on the skin of cheeks and ears. The extensor surfaces were more involved than the flexor surfaces of the extremities. The bend of the elbows and knees was free as were the soles and the vola manus. The diseased parts of the skin were dry, scaling and tender. No ulcers or crusts resulting from exudations were seen. The involved areas resembled lesions occurring after an overdose of roentgen-ray therapy. The hands were short and clumsy. The body was otherwise well proportioned. The scalp hair was sparse and fine, light blonde but not gray. The hairline on the forehead and neck was higher

than normal. *Endocrine features:* The thyroid was normal. Sella turcica was normal. The right testis was entirely absent; the left testis was pea-sized and not descended.

*Comment* There is no doubt that sister and brother, the sister described in 1928 by Siegrist, and the brother described in 1934 by A. F. Schnyder, exhibit Rothmund's syndrome in all its details of skin changes. It is of

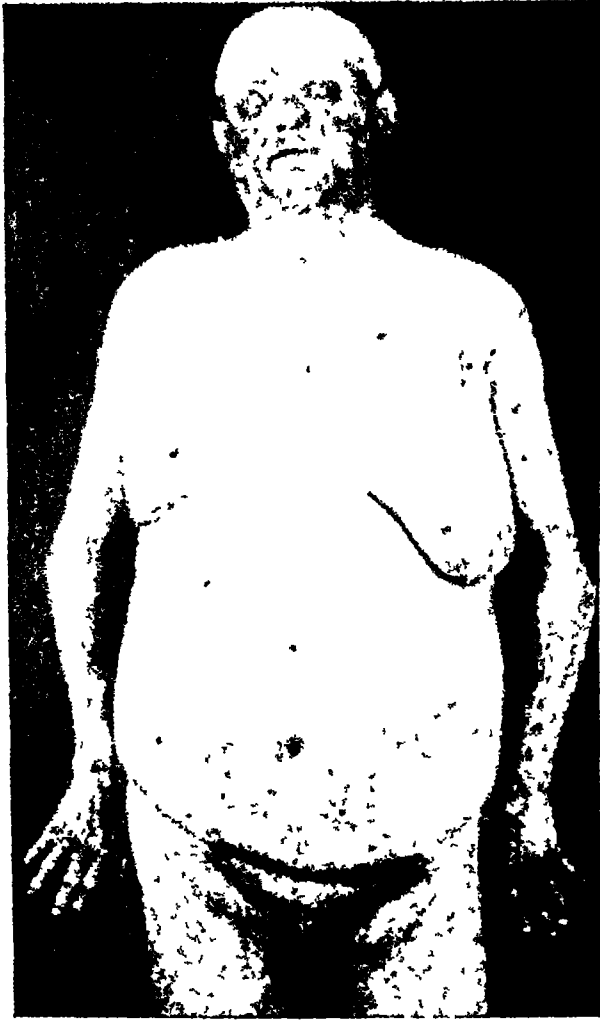


FIG 26 Case of a peddler. (Reproduced from paper by B. Bloch, H. Stauffer.) Appearance presenile. Thin arms in contrast to globulous abdomen. Very short hands. Skin of face, abdomen, and extensor surfaces of lower arms covered with telangiectases in net-like and round spot arrangement. Pendulant breasts. Genital organs underdeveloped.

interest that sexual retardation had been observed in the boy at the age of five. Canities was absent but the hair line of the boy was high in front and on the neck. The hands were short and the fingers clumsy, a feature not observed by Rothmund in his original description.

B. Bloch and H. Stauffer<sup>20</sup> in 1929 described three patients who belong to the syndrome under discussion. The title of their paper was "Skin diseases of endocrine origin, poikiloderma-like changes in connection with underdevelopment of the sex glands and dystrophia adiposogenitalis." The authors apparently were not acquainted

with Rothmund's or Werner's publications The second case is of special interest because of the detailed description of the appearance, illustrated by photographs, as well as the histological examination of the skin by such a dermatological authority as B Bloch The patient was a 40 year old peddler, of short stature In spite of a child-like face he looked old for his age There was no hereditary history At the age of four and a half years both eyes were operated upon for cataracts As a child he was sickly *Hair* was gray at 25 and sparse, the patient later was bald There were no pubic hairs This case was also presented by W Lutz, Swiss Dermatological

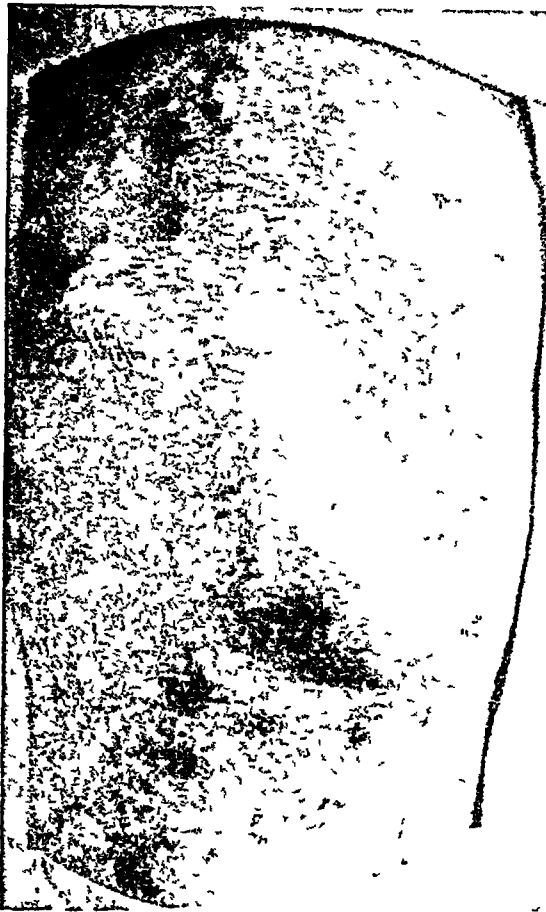


FIG 27 Knee. Round spots of telangiectases Yellowish to dark pigmented areas, intermingled with white depigmented areas

Congress, Basle, 1928 Obesity of chest and abdomen developed at 25 In contrast to the fat torso the extremities were strikingly thin, small and delicate and did not seem to fit the heavy torso The *extremities* were too short, the fingers almost like stumps *Muscles* and *subcutaneous fat* on the distal part of the extremities, in contrast to face and abdomen, were decidedly underdeveloped The hands and feet were particularly small The *skin* of the scalp was thin and tightly stretched Numerous irregular *pigmented* as well as *depigmented* spots were distributed over scalp, face, and extremities Areas of fine telangiectases were present in great numbers on the cheeks, the chin and the thorax They gave these parts a faded red color The *ears* were stunted, with only rudimentary lobes, and were covered with brown and white spots and numerous telangiectases There were no eyebrows The eyelashes were



represented only by an occasional hair. The face was devoid of hair. The skin of the trunk was scaling, dry and plainly atrophic. The vein could be seen through the atrophic skin. The atrophy was diffuse in some areas, in others more circumscribed. Telangiectases were present here as well as there, especially below the umbilicus. The skin over the extremities, especially on the extensor surfaces, was changed in a similar manner, even more markedly than on the trunk. Areas of telangiectases were noted mainly on elbows and knees; yellowish to dark pigmented spots were intermingled with white depigmented areas. Numerous hyperkeratotic areas on wrist and palm, as well as on the soles, were present. The hyperkeratotic spots had peculiar hollows in their centers. Those of the feet resembled oyster shells. The nails on fingers and toes were markedly altered, partly missing, partly only horny scales remained. There were no hairs on the extremities. A few stunted, straight hairs were on the pubic region. *Endocrine features.* The voice was unchanged. Libido appeared at 16. External genitalia were underdeveloped. The patient was heterosexual, and had never had intercourse. The penis was infantile, 3 cm long. The scrotum was the size of a walnut. Testicles as large as beans could be pushed back into the abdomen. Sella turcica was small. The thyroid was small, the left lobe showed a firm, smooth nodule about the size of a nut. According to the patient's statement only 30 teeth had developed. Some were rudimentary, the second incisors and the premolars were missing on both sides. Urine was normal. No blood sugar value was reported. Temperature was low, between 95° F. and 96° F. Pulse rate was normal. Reflexes were normal. Roentgenographic examination of bones showed atrophy (*osteoporosis*). The skull was thin, like that of a child. Definite arteriosclerosis was visible in the roentgenograms. *Histologic examination* of a biopsy specimen from a region above the right knee showed the following: "The horny layer was wider than normal throughout the entire section. The width of the epidermis was irregularly reduced, in some places only a few cell layers remained. Here the characteristic differentiation was no longer present. The basal cells were irregular and flattened, there was no spinous layer, and the boundary line between epidermis and cutis was straight. In other places the epidermis was broader, the differentiation of the layers was preserved, and the rete pegs and thin corresponding papillae were present but had an irregular form and arrangement. In the atrophic places the pigment was missing, whereas in others, especially in the brown spots, it was clearly increased. The sweat glands and follicles were entirely absent. The connective tissue of the cutis was unchanged. The elastic fibers were generally well developed, but in some papillae they were clumped, whereas in others only a few were present. In the papillae and in the pars reticularis there were greatly dilated capillaries. At one place in the wall of a blood vessel there was a deposit of lime."

*Comment.* The case is of special significance because it showed those features in an adult patient which were described by Rothmund in children. There is little doubt that one is justified in including B. Bloch and H. Stauffer's case in Rothmund's syndrome since the patient had cataracts at the age of four and a half and the skin changes also began at an early age. The skin exhibited the same characteristics with telangiectases, scaling, pigmentation and depigmentation, as described by Rothmund. His appearance was similar to Maria Karethina Drexel, described by Rothmund as a child and reported by Seefelder at the age of 70, in his follow-up study of Rothmund's cases. The absence of a familial history in Bloch and Stauffer's case is probably due to the fact that the patient had already left home when a child and had always been on the road as a peddler or beggar.

Histological examination of the skin biopsy with modern staining methods also confirmed the observations made with primitive methods by Rothmund, 62 years ago. B Bloch and Stauffer apparently did not know of Rothmund's original description. In respect to the classification of the skin changes, the authors made the following important statement: "There were no marked inflammatory and no *scleroderma-like* or *myxedema-like* changes." "A classification with *poikiloderma atrophicans vasculare* which Jacobi first described would perhaps seem the most plausible. However, there are some objections to this, the telangiectases and, also, to some degree, the atrophy, are much too slight in comparison with typical cases. As can be seen in the photographs and models, the changes in the pigment here are (*poikiloderma atrophicans vasculare*, Jacobi<sup>30</sup>) of foremost importance and, in addition to the dry and atrophic consistency of the skin, are outstanding in the clinical picture. Moreover, as has been clearly shown in his detailed summary of the literature on this subject the term *poikiloderma* is not applied to a sharply defined pathologic entity, but rather a group of variable symptoms. It becomes evident, when one reads the literature on this subject, that different and dissimilar dermatoses have been grouped under this name only on account of their superficial resemblances. These diseases are even less an etiologic entity, so that the classification of an individual case in this group means little and does not aid us in regard to its pathogenesis. Our cases, also, differ from Jacobi's type in the high grade regressive changes of the hair, the nails, the follicular apparatus and the sweat glands."

B Bloch and H Stauffer in their attempt to connect *poikiloderma atrophicans vasculare* with primary endocrine disturbance collect and discuss cases in the literature in which *poikiloderma* was found together with endocrine symptoms. Cases reported by K M Bowmann and E C Clark,<sup>31</sup> L Wertheim,<sup>32</sup> and R Leginsky<sup>33</sup> are cited by Bloch and Stauffer as related to their own cases. The case published by L Wertheim had a pituitary tumor and *poikiloderma atrophicans vasculare*. The skin changes started late in life. There were no cataracts present. The case of R Leginsky had skin changes described as *poikiloderma vasculare atrophicans*, which also began late in life. No cataracts were present. This patient had a questionable atrophy of the pituitary gland. Both cases have in their history, in their general appearance and in their clinical symptoms very little in common with Bloch and Stauffer's patient. They do not belong to the group of Rothmund's syndrome. K M Bowmann and E C Clark's<sup>31</sup> patient, however, had diffuse atrophic skin changes, with telangiectases beginning in early life and involving the entire surface of the body, ulcers on hands and feet; amputation of some fingers and toes because of secondary infection, bilateral cataracts at the age of 38, sexual underdevelopment, early arteriosclerosis but no graying of the scalp hairs. The scalp hairs were abundant and dark. Basal metabolic rate was -14, blood sugar 87 mg per 100 cc, tolerance curve flat. The patient died at the age of 39. At autopsy the endocrine glands did not show any abnormality. The

histology of the skin was thought to be similar to poikiloderma atrophicum vasculare. The negative findings on examination of the endocrine glands certainly did not show any relation of the skin changes to endocrine disease. For the question under discussion, however, it seems of interest to consider whether or not the case of Bowmann and Clark belongs to Rothmund's or to Werner's syndrome since he had cataracts, atrophic skin changes with telangiectases and sexual underdevelopment, early arteriosclerosis and skin ulcerations with spontaneous amputations of fingers and toes. In fact this unique case exhibited features of Werner's as well as Rothmund's syndrome.



FIG 28 (Reproduced from paper by R. Seefelder) Net-like telangiectases surrounding small areas of whitish discolored skin

The ulcers on both legs, the late appearance of cataracts (not until the third decade of life), presenile appearance and the presence of premature arteriosclerosis are characteristic of Werner's syndrome, whereas the occurrence of telangiectatic scaling areas of the skin, together with pigmentation and depigmentation are considered to be significant of Rothmund's syndrome. It seems, however, to be more justifiable to group the case of Bowmann and Clark under the cases designated as Werner's syndrome, since the characteristics of Werner's syndrome predominated.

R. Seefelder,<sup>34</sup> from the Eye Clinic, University of Innsbruck, reported in an excellent paper "Über familiares Auftreten von Katarakt und Poikilodermie," a family of six children, two of whom had skin changes with telangiectases and bilateral cataracts, in one only skin changes were noted, and two were healthy. Seefelder recognized the complete similarity of these cases to those reported by Rothmund in

1868 The parents were second cousins. The family lived in one of the completely secluded valleys of South Tyrol, called Val di Non (Nonsberg), which in its seclusion was completely analogous to that valley where Rothmund's children lived. The skin changes, which were described as identical, developed in all three affected children at from six to 12 months. They were localized on the face, with the exception of the forehead, on the ears, extensor surfaces of upper and lower extremities, and later they developed on the nates and on the flexor surfaces of the extremities. The arrangement of the lesions was symmetrical. The lesions consisted of small areas of whitish discoloration of the skin surrounded by reddish lines of a net-like appearance. The whitish lesions of pea size represented islets of normal but depigmented skin. The reddish network resulted from an atrophy of the skin. On these areas the skin was slightly depressed and resembled tissue paper, and was somewhat scaling. The red color was due to the fact that atrophic skin becomes translucent and thereby the subcutaneous tissue with its blood vessels was readily visible. Areas of pigmented and depigmented skin were intermixed. Telangiectases were present on face and on the back of the hands. The mucous membranes were not involved. The scalp hair and the nails were normal. The diagnosis of the Skin Clinic (University of Innsbruck) was *poikiloderma atrophicans vasculare (Jacobi)*<sup>30</sup>. Cataracts rapidly developed at the age of three years in both children and operations were successfully performed. *Endocrine features*. At the age of 12, when the boy was examined, neither testis was descended.

*Comment*. The similarity of these three children to those described by Rothmund is obvious. The kind as well as the localization of these lesions is identical with the Rothmund type of syndrome under discussion. As in the case described by Schnyder, retardation of the sexual development was marked. R. Seefelder, in agreement with Rothmund, considered the syndrome as a recessive heredofamilial disorder.

*A. Marchionini and L. Lux*,<sup>35</sup> in 1937, described under the heading "Juvenile Katarakt bei Skleropoikilodermie," the case of an unmarried woman, 30 years old. She exhibited bilateral cataracts, scarce fine grayish scalp hairs and a high hairline (photograph). Menstruation had been regular but painful. The genital organs were atrophic. Pubic hair was very scarce. The fasting blood sugar was high and sugar tolerance curve was characteristic of potential diabetes. Basal metabolic rate was normal. Pigmented and depigmented spots were seen on the skin of the face, on the extensor surfaces of the lower arms and hands. Telangiectases and pea-sized red spots were noted on the face and arms. The skin was in some places indented, shiny and atrophic. A histologic picture of the skin showing hyperkeratosis and an atrophic epidermis was included in the report. The pars papillaris was flat. The author reported a band-like homogenization of the upper layer of the collagenous connective tissue, but this was not evident in the photograph. The subcutaneous tissue was rather loose. The vessels, i.e., the veins, were distended and formed little pools.

Marchionini and Lux classified this lesion as scleropoikiloderma on the basis of the dermatological syndrome described by Jaffe<sup>36</sup> who believed that scleropoikiloderma has features of scleroderma and poikiloderma without being identical with either of these diseases. Marchionini and Lux were not familiar with the original publications of either Rothmund or Werner and, therefore, assumed that their case represented an unknown new syndrome. However, the patient exhibited skin changes identical with the cases described by Rothmund, Siegrist, Schnyder, Bloch and Stauffer and See-

felder. Although cataracts did not develop in this case until the age of 30, it seems justifiable to group the case under Rothmund's syndrome because of the characteristic telangiectatic skin changes occurring simultaneously with atrophy of the epidermis in the afflicted areas and because of the absence of ulcers and arteriosclerosis. As etiological factor Marchionini and Lux suggest "an ectodermal abnormality, which is released by a pluriglandular insufficiency." Such a sequence of events is not, to our knowledge, known in pathology.

#### OWN CASE

Patient Sch was observed 15 years ago and described as "Acromiery with deformities of small phalangeal joints."<sup>17</sup> At that time I was not familiar with Rothmund's syndrome.

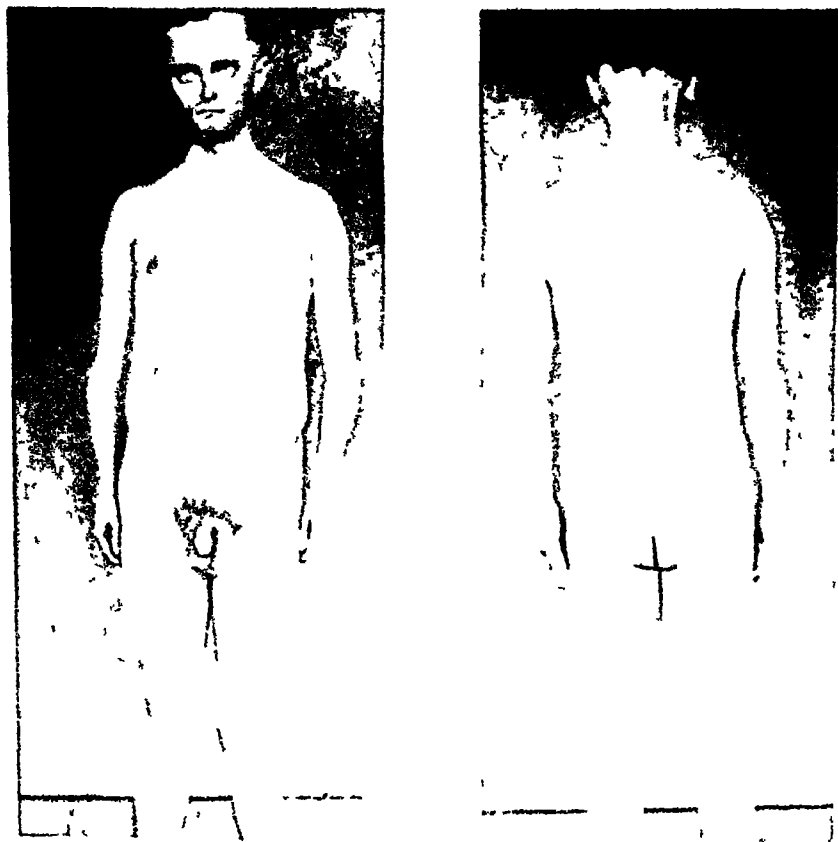


FIG 29 Case Sch. Short stature. Small nose and chin, receding hairline, especially at sides and back of head. Short upper arms and legs. Knock-knees. Scarce pubic hair.

Patient Sch was 20 years old. No pertinent family history was given. He reported that as a child he had a peculiar reddish, scaling skin on some areas of his body. The skin changes never bothered him. He always felt tired. He came to the hospital because he could not earn a living. His hands were so short and deformed he was unable to work as a laborer. *Appearance.* He was short in stature, 150 cm. His weight was normal. His face did not give the impression of presenility and the appearance of his face corresponded to his actual age. His arms and legs were short. There was an obvious contrast between the lean and short extremities and the normally formed chest and abdomen. He stood and walked with knocked knees.

The feet, and especially, the hands, were very small, the fingers were short, plump and deformed like those of an arthritic person. The motion in the phalangeal joints was slightly limited. The scalp *hairs* were scarce and fine. Over the frontal bone he was almost bald. The hair line in the occipital region was higher than normal. Eyebrows and eyelashes were normally developed. He had a downy beard of fine hairs. He had only a few hairs on chest and abdomen. The axillary hairs were almost absent. The pubic hairs were underdeveloped, coarse and not curled. Symmetrically distributed on both cheeks and on his nose, were small areas of whitish discoloration which were surrounded by reddish lines of the color of telangiectases. The whitish

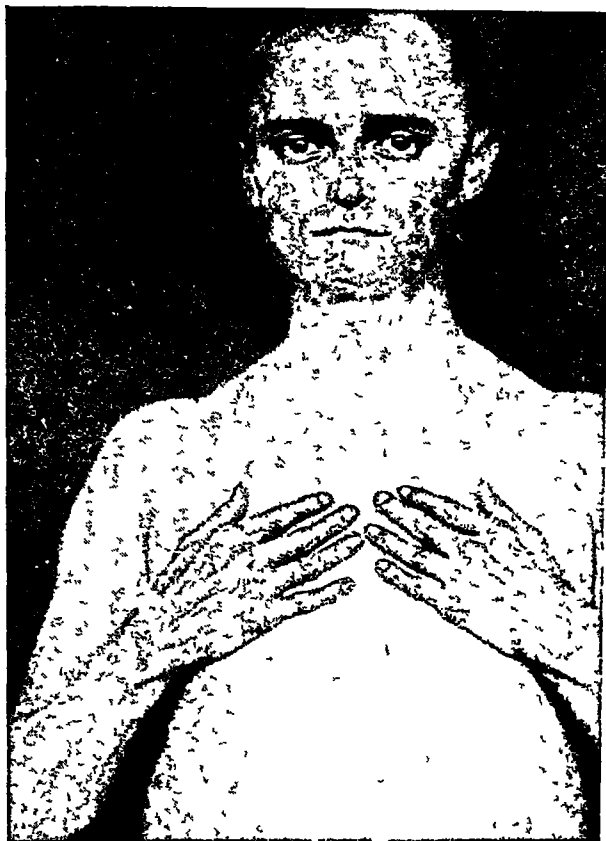


FIG 30 Net-like telangiectases visible on face, nose, hands, and both sides of abdomen

areas were scaling and slightly depressed. Also, simple telangiectases in diffuse arrangement were visible. The forehead and the ears were not affected. The skin was rather thin but not taut nor stretched. The mucous membranes were not involved. The same skin changes consisting of areas of whitish discoloration surrounded by a net-like arrangement of telangiectases were noted, especially on the arms, hands and to a minor degree on the lower legs, mainly located on the extensor surfaces of the extremities. Areas of telangiectases were also present on the skin of the lateral parts of the abdomen and symmetrically on both nates. The color of the skin of the affected parts was of a reddish hue, but surrounding the small areas of discoloration, pigmentation in net-like arrangement, apparently in connection with the telangiectases, was observed. The pigmentation was light brown in color and not impressive. The most impressive feature of the skin was the telangiectases and

the pliability of the atrophic skin. A taut, stretched skin was not observed on any part of the body. There were no circumscribed areas of hyperkeratosis and no skin ulcers were present. The subcutaneous fat tissue and the muscles were somewhat underdeveloped on the lower arms and hands. On the lower legs and feet these tissues were also reduced, but not to such a degree as on the upper arms and hands. Nails on hands and feet were normal. On roentgenographic examination the bones of the hands and arms appeared normal for his age. No osteoporosis was seen. The spaces of phalangeal joints of the short fingers were narrowed. There were no changes in the bones themselves. The deformities of the short fingers were probably due to



FIG 31 Small hands and deformed short fingers. Linear and net-like telangiectases.

changes in the periarticular tissues. His *nose* was small. His *chin* was short. His *voice* was high but not hoarse. His *teeth* were all developed and in good condition. His *ears* were normal in shape. *Eyes*. The patient himself did not complain of visual disturbances, but both lenses showed beginning *opacities* at the lower poles. The lungs and the circulatory organs were normal. Blood pressure was 125 mm Hg systolic and 80 mm diastolic. No signs of arteriosclerosis were found. *Endocrine features*. The external genitalia were fairly well developed. Both testes were, however, small in size. The prostate was small. Sexual desire was present.

*Comment*. The skin changes in our patient had already developed in early childhood as they did in Rothmund's cases. They consisted of small areas of atrophic scaling epidermis surrounded by net-like telangiectases. Since these were characteristic of the skin lesions reported in all cases of Rothmund's syndrome one is justified in diagnosing this case as one of Rothmund's syndrome, in spite of the fact that cataracts did not develop until the age of 20. In Rothmund's original eight cases Karolina Drexel (see page 597) did not develop cataracts. In Nieden's and in Marchionini's case the cataracts developed also at the age of 20 (see pages 601 and 607). Small

hands and feet and short deformed fingers are not observed in all cases of Rothmund's syndrome. This symptom was noted by Seefelder, in the follow-up study of the children originally described by Rothmund, in two instances (see page 607). It was also present in the case of Bloch and Stauffer (see page 602) and in one of the children described by Seefelder (see page 600) as it was observed in our case.

*Summarizing*, the observations which establish *Rothmund's syndrome* as a clinical entity, it is evident that the skin changes are the most characteristic features for differential diagnosis and are present in all cases reported. In contrast to Werner's syndrome the skin is not taut and not tightly stretched over the atrophic underlying structures, but is thin and pliable. Ulcerations are not observed. Marmorization of the skin, due to distended veins and known as livedo-cuticularis in later stages develops to form the characteristic net-like arrangement of the telangiectases around the atrophic scaling area. Owing to formation of telangiectases, the color of the affected skin impresses one as pinkish red, but on closer inspection small white, atrophic areas and brownish pigmented spots are seen in the vicinity of the telangiectases. Since similar features are seen in poikiloderma atrophicans vasculare (Jacobi<sup>30</sup>) the skin lesions in Rothmund's syndrome were also classified as poikiloderma atrophicans vasculare or as scleropoikiloderma. B. Bloch (see page 602) has objected to such a classification, since in poikiloderma atrophicans vasculare telangiectases as well as pigmentation are much more extensively developed and at the same time inflammatory changes in the subcutaneous tissue are found. In the skin lesions of Rothmund's syndrome neither inflammatory reactions (as in poikiloderma atrophicans) nor homogenization of the subcutaneous tissue (characteristic of scleroderma) is found. For this reason the classification as "poikiloderma" or "scleropoikiloderma" is neither in agreement with the histological findings nor with the familial occurrence of this disorder. It seems more appropriate to designate the skin disorder with the purely descriptive term of "heredofamilial atrophic dermatosis with telangiectases" in accordance with the designation of the skin changes in Werner's syndrome as "heredofamilial atrophic dermatosis with skin ulcers."

### III DISEASES RELATED TO WERNER'S SYNDROME (PROGERIA OF THE ADULT), AND ROTHMUND'S SYNDROME

(A) *Cataracta dermatogenes (Neurodermitis) type Andogsky*. N. Andogsky<sup>38</sup> in 1914 published, under the title "Cataracta dermatogenes," reports on four single and unrelated individuals. These people had suffered from a chronic eczemoid skin lesion from childhood and in the third decade of life developed bilateral cataracts. Similar cases were later published by A. Vogt,<sup>39</sup> A. Lowenstein,<sup>40</sup> A. Siegrist,<sup>27</sup> H. Ollendorf and G. Levy,<sup>41</sup> H. J. Oltmann,<sup>45</sup> Lasló,<sup>43</sup> A. Franceschetti,<sup>46, 47</sup> Metzger.<sup>42</sup> To these 15 cases Ivar



Kugelberg<sup>44</sup> has added two more cases in an extensive survey of this subject.\* A. Lowenstein<sup>10</sup> prefers to classify the skin lesions as "neurodermitis," a skin disorder for which, according to I. Kugelberg,<sup>44</sup> the names of ekzema numulare, ekzema en plaques, dermatitis lichenoides pruriens, lichen circumscriptus chronicus (Vidal), pruritus diathésique (Besnier), are found in the literature. Neurodermitis is, according to Kugelberg,<sup>44</sup> a chronic eczematous skin disorder which after childhood develops eczema or complicates ichthyosis. It may also develop independently. The intensity of the inflammation may be marked or slight. Such a process produces lichenification of the skin, neck and the flexor surfaces of the extremities, especially the bend of elbows and knees. The skin in the bends shows a peculiar square formation ("Grobe Fekderung," "chagrinization"). In some cases a facies leontina may result from the skin disorder. A histological examination of a skin biopsy is not reported. In some cases asthma and eosinophilia are described. Heredity is reported in only one case of I. Kugelberg<sup>44</sup>. The family tree of this patient showed five generations in which ichthyosis alone, ichthyosis and neurodermitis and asthma occurred interchangeably. Only one member out of the 50 forming the genealogical tree exhibited the combination of ichthyosis, neurodermitis and cataracts.

This case, a boy of 15, had had eczema from the age of six months. At the time of his examination the skin was dry and tight. Fine scales were noticed over the whole body. On the abdomen and shoulders typical ichthyosis was found. Lichenification of the skin was remarkable on the forehead, cheeks and extremities. *Height* was 145 cm. *Teeth* Two incisors had never developed. *Hair* Scalp hair was abundant and normal. No pubic hairs were visible. *Eyes* Bilateral cataract. *Endocrine features* The thyroid was normal. Basal metabolic rate +10. Calcium was 13.3 mg per cent. Roentgen-ray examination revealed normal bones, normal epiphyses and normal sella turcica. Fasting blood sugar was normal. Sugar tolerance was normal. The penis and scrotum were very small and underdeveloped.

*Comment* It is possible that this group of patients with juvenile cataracts and features of ichthyosis and neurodermitis may also represent a heredofamilial dermatosis with occasional cataracts. It is, however, evident from the features described as characteristic of Werner's syndrome, as well as of Rothmund's syndrome, that the group of "Cataracta dermatogenes" with neurodermitis differs from these syndromes. Even the heredofamilial occurrence of cataracta dermatogenes with neurodermitis may be doubted since only one case out of 17 had stigmata of heredity.

(B) *Progeria of children with nanism (Hutchinson-Gilford's syndrome)* Progeria of children (Hutchinson<sup>48</sup>-Gilford's<sup>49, 50, 51</sup> syndrome), also called "nanism senile" or "progero nanie," is a disorder which develops from a few months to three years after birth. In the cases reported the children were normal at birth. There was no history of familial occurrence.

\* Ten other cases which belong to these groups were described under the title "Atopic Cataracts" by William P. Beetham, Arch. Ophth., 1940, xxiv, 21.

of this disorder or of inter-relationship of the ancestors. The main clinical features observed almost uniformly in all cases were as follows. All the children with progeria looked alike. The published photographs look like the pictures of twins.

All patients were dwarfed in stature. The skull was large in comparison with the face. The frontal and parietal bones were unduly prominent. The fontanelles closed early. The scalp hairs were present at birth but became grayish and scarce, and completely disappeared in the course of the disease. There was either very little or no development of the eyebrows. The eyelashes were rare or absent. The faces of these children resemble that of a newly hatched bird. The ears were small, flat, not lobulated, and protruded from the head. The skin of the scalp and face was thin



FIG 32 (Reproduced from paper by W. A. Manschot) Patient normal at age of one year

and of a waxy color. In some areas the skin was taut. The same condition of the skin prevailed on most parts of the body. In some parts, especially over the dorsum of the hands, the atrophic skin was wrinkled like tissue paper. On the thorax and abdomen sharply defined and pigmented areas were seen. There were no ulcers of the skin. The subcutaneous fat on the extremities was poorly developed or almost absent. This was in contrast to the globulous abdomen, where the subcutaneous fat was plentiful. The umbilicus was obliterated. The chest was small. The ribs were prominent and thin. The extremities were short, especially the hands. The feet were flat and small and the fingers were short. Deformities of the phalangeal joints, the knee joints and the ankle joints resembled those of arthritis. The gait of the patient was shuffling as a result of the deformed joints and the tightly drawn skin of the extremities. The muscles on all extremities, like the subcutaneous fat tissue, were poorly developed. The nails were short and crumbly. Proptosis of the eyes simulated true exophthalmos. There was no early cataract observed in the cases published (*V. T. Curtin and H. F. Kotsen*,<sup>32</sup> *E. C. Mitchell and D. W. Goltmann*<sup>23</sup>).

The nose was small and beaked like that of a bird. The chin was retracted. There were isolated, symmetrical fat patches on the lower part of the cheeks and also beneath the mandible, which contributed much to the bizarre aspect of the otherwise taut skin of the face and forehead. The teeth were irregularly placed and carious. The thyroid was not enlarged and not easily palpated. There were normal breath



FIG 33 Patient of Manschot at age of 15. Enlarged hairless scalp, no eyebrows, protruding ears, small mouth. Taut skin, prominent deformed joints of hands and knees. Muscles and fat tissue of both extremities atrophic in contrast to globulous abdomen. Umbilicus obliterated. Sexual underdevelopment.

sounds, and no râles were audible. The heart was normal during the first decade, but in the cases living over 10 years enlargement of the heart was noted simultaneously with a rise in blood pressure. The individual with the longest lifetime of these cases of "progero-nanie" was a 26 year old male reported in the Dutch literature by *W. A. Manschot*<sup>54</sup>. This patient had diffuse arteriosclerosis combined with calcification

of the heart valves His blood pressure at the age of 11 was 110 mm Hg systolic and 85 mm diastolic, at 18, 132 mm Hg systolic and 90 mm diastolic, at 26, 180 mm Hg systolic and 120 mm diastolic At 26 he suffered from cardiac asthma and angina pectoris and died of cardiac insufficiency as a result of arteriosclerotic heart disease Liver and spleen were not enlarged as long as the circulation was normal In later years the liver was found enlarged and the spleen also became palpable (congestion of the liver with slight cirrhosis was found at autopsy) The genital organs were



FIG 34 Patient of Manschot at age of 26

normal in the younger cases but in the adolescent cases they were noted as small Pubic hairs were almost absent Roentgenograms of the bones showed a characteristic elongation of the necks of the femur (*E C Mitchell and D W Goltmann*<sup>53</sup>) Osteoporosis was found in some areas, in other places, as in the cortex of the femurs, increased density of the bone was seen The epiphyseal lines were prematurely closed Sella turcica was of normal size Red and white blood cells were normal Basal metabolic rate was normal The sugar tolerance curve was flat Serum calcium and serum phosphorus were normal

Three autopsies on cases of progeria were reported (*H Gilford*,<sup>50</sup> *J Orrico and F Strada*,<sup>55</sup> *W A Manschot*<sup>54</sup>) The main finding was diffuse calcification and sclerosis of the blood vessels H Gilford reported an enlarged thymus, Orrico and Strada found a little cyst in the pars intermedia of the pituitary *W A Manschot*<sup>54</sup> believed that the number of eosinophiles in the pituitary was reduced Other than the

diffuse arteriosclerosis, however, there were no definite lesions of inner organs and endocrine glands evident which could have explained the bizarre appearance of these patients.\*

*Comment* There is a certain similarity in the features of "Werner's syndrome" and "progeria with nanism" in children. The cases exhibiting Werner's syndrome are short, almost dwarfed in stature. In progeria of children the patients are definite dwarfs. In both syndromes the extremities are short and the abdomen disproportionately large. The fingers and toes are short, and the joints of the extremities are deformed in both instances. The skin is atrophic and taut on the extremities. The panniculus adiposus of the forearm and lower legs is poorly developed as are the muscles, in both disorders. The lack of hair is more pronounced in progeria of children than it is in Werner's syndrome. Sexual retardation is present in both syndromes. Diffuse arteriosclerosis, osteoporosis and the premature senile appearance are the most impressive features present in Werner's syndrome as well as in progeria of children. The autopsy findings in both syndromes are diffuse arteriosclerosis and no definite changes in endocrine organs. Progeria of children, however, differs from Werner's syndrome as follows: (1) There is no familial occurrence. (2) There are no pressure ulcers of the skin. (3) There are no cataracts. (4) The abnormal features develop in early childhood in progeria of children, whereas in Werner's syndrome they become evident in the second decade of life.

It is suggested that progeria of children and Werner's syndrome result from multiple germ plasm defects manifesting themselves at different ages in abiotrophic features of the genotypic kind.

(C) *Myotonic dystrophy* Myotonic dystrophy was first differentiated by I. Hoffman<sup>56</sup> from "congenital myotony" as a separate clinical entity in 1900. It was Steinert,<sup>57</sup> however, in 1909, H. Curschmann,<sup>58</sup> A. Hauptmann,<sup>59</sup> and especially O. Naegeli<sup>60</sup> and his pupil K. Rohrer,<sup>61</sup> who conceived the clinical picture of myotonic dystrophy as a general dystrophy in which the myotonic reaction is not an essential feature of the syndrome. It may even be absent, and only wasting of the entire body and weakness of some muscles may be evident. It was quickly recognized that premature aging, loss of scalp hair, especially on the forehead, atrophic, glossy skin of tissue-like consistency on forearms, hands and lower legs, early cataracts, diminished sexual functions and testicular atrophy are as important in the features of the disease as wasting of some muscle groups or myotonic reaction. In many instances a heredofamilial tendency of the disorder was reported and, especially, the collateral occurrence in brothers and sisters of one generation was observed. K. Rohrer reported an hereditary factor in 23 out of 82 cases. In a complete review of 35 cases in the literature and 15 cases of his own observation, he also emphasized that general weakness,

\*While this paper was in press N. B. Talbot, A. M. Butler, E. L. Pratt, E. A. MacLachlan and J. Tannheimer published an article on Progeria of children with metabolic studies and an autopsy report, *Am. Jr. Dis. Child.*, 1945, lxi, 267.

wasting of the subcutaneous fat tissue, skin atrophy, loss of scalp hairs, sexual dysfunction, testicular atrophy, are as characteristic of myotonic dystrophy as atrophy of some muscle groups with occasional myotonic reaction. One of K Rohrer's cases may be quoted as especially informative in this respect and in view of the relationship of Werner's syndrome to muscular dystrophy.

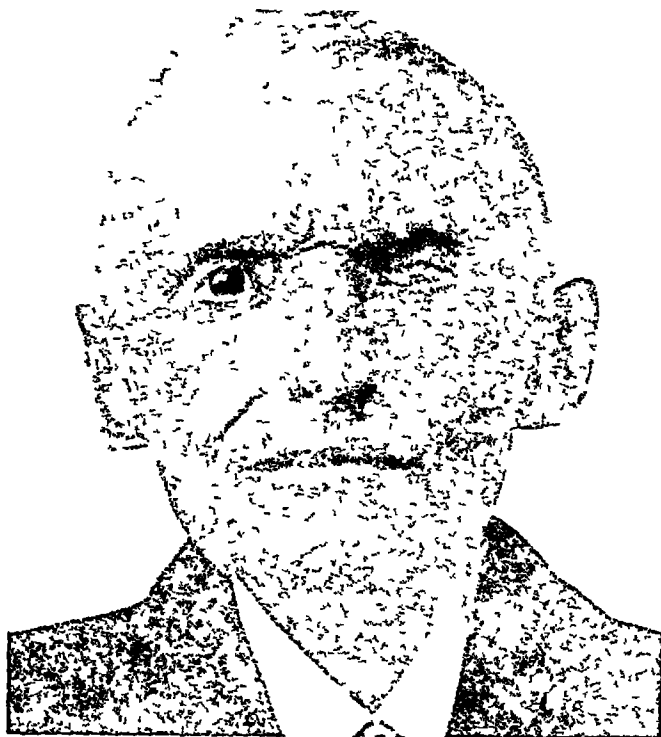


FIG 35 (Reproduced from paper of K Rohrer) Presenile appearance. Protruding ears. Cataracts.

The patient was a 53 year old male. Height was 162 cm. His appearance was atrophic and slender. Subcutaneous fat had almost disappeared. Atrophic skin had been noticed for a long time. At the age of 33 ulcers which did not heal were noted on both lower legs. (His brother also had ulcers on both legs.) There were no varicosities. Some yellowish pigmentation was seen on the flat ears which protruded laterally from the face. Also yellowish patchy pigmentation of the skin of the abdomen was seen. Scalp hairs turned gray very early and were sparse at the time of examination. Pubic hairs were rare. Muscle power of both forearms and hands was diminished after the age of 45. No myotonic reaction was found. Tendon reflexes were normal, but an Achilles tendon reflex could not be elicited because of an ulcer on that tendon. At the time of examination he was only able to do very light work. Both feet were unusually flat. Bilateral cataract was noted at the age of 42. Voice was high-pitched. The heart was normal in size. Blood pressure was 160 mm Hg systolic. Arteries were slightly tortuous. He married at the age of 26 and had two healthy sons. For several years he did not have any sexual desire.

*Comment* It may be granted that in most of the cases of myotonic dystrophy the muscular dystrophy and the myotonic features are the out-

standing features of the disease. General dystrophy and endocrine symptoms may be less evident. Some cases of myotonic dystrophy, however, as the patient reported by Rohrer, demonstrate the close relationship of myotonic dystrophy to Werner's syndrome. It may be mentioned that an outstanding neurologist who examined one of our cases (Sidney O.) ventured the diagnosis of myotonic dystrophy in this case of obvious Werner's syndrome, although myotonic features were absent.

(D) *Hereditary ectodermal dysplasia, dystrophy of hair and nails* (Type McKay and Davidson). As hereditary ectodermal dysplasia of the "anhydrotic type"<sup>61</sup> (Type Widderburn) an anomaly is described, which is characterized by complete inability to sweat (anhydrosis), a deficiency of the scalp, axillary and pubic hair (hypotrichosis), and incomplete development of the teeth (anodontia). This type is restricted as to sex and only males are affected. From this anhydrotic type of ectodermal dysplasia McKay and Davidson<sup>62</sup> differentiate a group in which the sweat and sebaceous glands are present and perspiration occurs but hair and nails are dystrophic. In these cases keratoderma plantaris et palmaris is observed. The skin is otherwise normal in appearance. This type, in contrast to the anhydrotic type, is transmitted by both sexes and manifests itself through many generations<sup>63</sup>. The hyperkeratosis plantaris, the loss of scalp hairs, bear some similarity to Werner's syndrome. The differentiation is obvious, however, since neither general dystrophy of the body, cataracts nor presenility is observed in "hereditary ectodermal dysplasia". In this syndrome the clinical features result only from a defect of the ectodermal germinal layer, whereas in "Werner's syndrome" and even more obviously in "progeria of children" multiple defects of the germ plasma produce various abiotrophic changes of organs deriving not only from the ectoderm but also from the other germinal layers.

#### GENERAL COMMENT

As seen from various publications quoted from the world's literature, there is considerable confusion in recognizing Werner's and Rothmund's syndromes as different although related clinical entities. This is the more astonishing for the striking resemblance of cases of one family affected with one of the syndromes to cases of another family. The striking differences of Werner's syndrome and Rothmund's syndrome are as follows.

(1) Werner's syndrome starts at the age of 20 to 30, beginning with graying of the hair. Later skin changes and cataracts develop. Rothmund's syndrome begins in early childhood. The skin changes are already visible three to six months after birth. Cataracts develop also in childhood, namely, from three to five years of age.

(2) The *shortness of stature* is more outstanding in Werner's syndrome than it is in Rothmund's syndrome.

(3) The *skin changes* are different in their features in both syndromes. In Werner's syndrome the most striking feature is tightening of the skin.

| Symptoms  | Werner's Syndrome | Rothmund's Syndrome | Cataracta Dermato-<br>genes<br>with<br>Neuro-<br>dermitis | Progeria of<br>Children<br>with<br>Nanism | Myotonic<br>Dystrophy | Ectodermal<br>Dysplasia<br>with<br>Dystrophy of<br>Hair and Nails |
|---|-------------------|---------------------|---|---|-----------------------|---|
| Heredofamilial occurrence                       | +++               | +++                 | ±   | 0   | ++                    | +++   |
| Age at the beginning of disorder                | 20-30 y           | 3 mo-3 y            | 3-20 y  | 2-5 mo                                    | 20-30 y               | shortly after birth   |
| Shortness of stature                            | +++               | +                   | 0   | ++++                                      | +                     | 0   |
| Skin changes                                    | +++++             | +++++               | +++++   | +   | +                     | ++  |
| a) Tightly drawn over underlying tissue         | +++++<br>20-30 y  | 0                   | 0<br>3-20 y   | +<br>2-5 mo                               | +<br>20-30 y          | 0<br>shortly after birth  |
| b) Atrophic and thin skin                       | +++++             | ++                  | ++  | ++  | ++                    | +   |
| c) Telangiectases                               | +                 | +++++ 3 mo          | 0   | 0   | 0                     | 0   |
| d) Scaling                                      | ++                | +++++               | +++++   | +   | 0                     | 0   |
| e) Pigmentation and depigmentation              | +                 | +++                 | ++  | +   | +                     | 0   |
| f) Ulcers                                       | +++++             | 0                   | 0   | 0   | +                     | 0   |
| Cavities of scalp hairs<br>Age                  | +++++<br>20-30 y  | ±<br>40 y           | 0   | +++++<br>2-5 mo                           | +++++<br>20-30 y      | Bald  |
| Sparse sex hairs                                | +++               | ++                  | 0   | +++                                       | +++                   | 0   |
| Muscular atrophy on distal parts of extremities | +++               | ±                   | 0   | +++                                       | +++                   | 0   |
| Atrophy of the subcutaneous fat tissue          | +++               | ±                   | 0   | +++                                       | +++                   | 0   |
| Bilateral cataracts                             | +++++<br>20-30 y  | +++++<br>3-4 y      | ±   | 0   | +++++<br>20-30 y      | 0   |
| Diffuse arteriosclerosis                        | +++               | ±                   | 0   | +++++                                     | ++                    | 0   |
| Osteoporosis                                    | +++               | 0                   | 0   | ++  | +                     | 0   |
| Joint deformities                               | +++               | +                   | 0   | +++                                       | +                     | 0   |
| Thyroid   | +                 | 0                   | 0   | 0   | +                     | 0   |
| Proptosis                                       | +++               | 0                   | 0   | +++++                                     | 0                     | 0   |
| Sexual underdevelopment                         | +++++             | ++                  | 0   | +++                                       | +++                   | 0   |
| Myotonic reaction                               | 0                 | 0                   | 0   | 0   | ++                    | 0   |

over the underlying structures which are very poor in subcutaneous fat tissue. The skin changes are localized on the lower legs and feet and, to a lesser degree, on the forearms, hands and face. The ears are only slightly deformed and there is little involvement of the skin over the ears. Circumscribed hyperkeratotic areas of shell-like appearance are present on the soles beneath the great toes and heels. Ulcers develop mainly on the points of pressure on heels and toes, over the ankles and, especially, over the Achilles tendon. The fact that skin can be successfully grafted on the ulcerated areas demonstrates that the ulcers are not entirely trophic in origin but due to pressure on areas where the skin is tightly drawn over the bone without any padding of subcutaneous fat tissue. The classification of these skin disorders in the literature as "scleroderma" or "scleropoikiloderma" does not correspond to the clinical or histological findings. The characteristics of true



scleroderma, namely, sclerosis of the skin and homogenization of the subcutaneous tissue, are not present, but there is atrophy of the skin, flattening of the rete and of the papillae. The most impressive feature, however, is the poorly developed panniculus adiposus beneath the involved areas in the distal parts of the arms and legs. It seems that the disappearance of the subcutaneous fat tissue which apparently occurs simultaneously with the atrophy of the superficial layers of the skin results in tightening of the skin over the underlying structure and simulates scleroderma. Inflammatory changes of the blood vessels (arteries) which are found in true scleroderma are not present. Calcium deposits in the walls of the subcutaneous blood vessels, however, are seen in the most progressed cases. Since the skin changes in Werner's syndrome only simulate true scleroderma but are in no way identical with this disease, the classification as scleroderma should be rejected. A descriptive name as "heredofamilial atrophic dermatosis with skin ulcers" seems to be more appropriate.

In Rothmund's syndrome the skin lesions are in evidence five months after birth. In contrast to Werner's syndrome there is neither stretching of the skin nor the presence of ulcers. The first changes occur on the skin of the face, ears, on the cheeks, on the buttocks, and later the skin over the knees and extensor surfaces of the extremities is involved. The flexor surfaces show lesions late, or not at all. The vola manus and the bend of elbows and knees remain free. In the first stages the skin changes correspond to the livedo reticularis and exhibit, therefore, a reddish hue. Reddish striae, round reddish spots with telangiectases appear later on. The color of the lesion changes to a yellowish scar tissue which scales slightly. Normal skin encircled by such yellowish scar tissue acquires a characteristic areolated appearance. The areas of the skin not involved are extremely fine, soft, and translucent, causing the smallest ramifications of the skin veins to become visible. The skin on the hands and feet is pliable and thin as tissue paper. Some scattered telangiectases are also seen in these areas. Pigmented and depigmented areas are more pronounced than in Werner's syndrome. The classification of these skin changes as scleropoikiloderma does not coincide with the features described. A descriptive designation of the skin lesions in Rothmund's syndrome as "heredofamilial atrophic dermatosis with telangiectasis" seems more appropriate.

(4) Histological examination of the skin shows, in both cases, atrophy of the mucous layer, flattening of the papillae, even complete disappearance of the rete pegs. The changes typical of scleroderma and scleropoikiloderma were absent, there were neither inflammatory changes of the subcutaneous tissue and of the blood vessels nor sclerosis or homogenization of the collagenous tissue. The difference between the histological changes in Werner's and Rothmund's syndromes is the distention of the veins. In Werner's syndrome only occasional distention of the veins is found in the subcutaneous tissue whereas in the affected parts of the skin in Rothmund's syndrome the veins are generally distended and may even form small pools.

(5) The *muscles* and the *subcutaneous fat tissue* of the distal parts of the extremities in Rothmund's syndrome are less atrophic than in Werner's syndrome. In childhood the muscles of Rothmund's syndrome are, in this respect, normally developed. In the few cases of Rothmund's syndrome observed at a later age muscular atrophy occurs on forearms and lower legs. Fingers and hands remain small and short in both syndromes.

(6) *Cataracts* are of the same kind in both syndromes. They develop as star-like opacities in the periphery of the lens, mostly on the posterior pole. However, the age at which the cataracts begin to develop is significant. In Rothmund's syndrome they are already formed in early childhood, that is, at the age of three to five, in Werner's syndrome they develop in adult life, between the age of 20 and 30.

(7) *Canities* is the earliest feature of Werner's syndrome. It appears in the early twenties. The children exhibiting Rothmund's syndrome have abundant scalp hairs of normal color, even in the cases observed at a later age canities is not an outstanding feature.

(8) Diffuse *arteriosclerosis* is evident in Werner's syndrome in all cases and results in early complications involving the circulatory system, such as gangrene or heart failure. In Rothmund's syndrome diffuse arteriosclerosis is not observed in young patients. Patients exhibiting Rothmund's syndrome in childhood may reach an old age, as Seefelder's follow-up study of Rothmund's cases shows. In some cases, however, as in Bloch and Stauffer's case, arteriosclerosis developed in the fourth decade of life.

(9) *Osteoporosis* occurred in all cases of Werner's syndrome in which roentgen-ray studies of the bones were made. In Rothmund's syndrome osteoporosis was not observed.

(10) Dysfunction of the *thyroid* was noticed in some patients exhibiting Werner's syndrome. In some patients a goiter was found, in some patients the thyroid could not be palpated at all. Symptoms of hyperthyroidism were not present in any of these patients. Proptosis of the eyes found in most of these patients is not due to hyperthyroidism. In Rothmund's syndrome dysfunction of the thyroid was not observed. These patients do not show proptosis.

(11) Underdevelopment of the *sex organs* and of the pubic hair is found in all cases of Werner's syndrome. In males, however, erections and the ability to have intercourse seem to have been preserved for some time. Most of the females described did not marry but had menstruated at least for some time. The patients exhibiting Rothmund's syndrome showed, in most cases, normal sexual development during puberty. In some male cases, however, retardation of sexual development and, later, atrophy of the testes was noted. Those females of the families described by Rothmund who exhibited both skin changes and cataracts were childless, whereas those females who had only skin changes produced children.

(12) The bizarre changes of the epithelium of the *vocal cords* causing a *hoarse, high pitched voice*, were found only in patients exhibiting Werner's

syndrome. High pitched voices may occur in Rothmund's syndrome due to sexual retardment but the characteristic changes of the surface of the vocal cords were never observed in cases with Rothmund's syndrome.

(13) Tendency to *diabetes* or diabetic glycosuria is observed in cases of Werner's syndrome but not in Rothmund's syndrome. The tendency to diabetes seems to parallel the progress of arteriosclerosis. The occasional observation of gangrene of the lower legs is the result of a secondary infection of the pressure ulcers but aggravated by the presence of arteriosclerosis.

The comparison of features of both syndromes under discussion shows that Werner's, and Rothmund's, syndromes are heredofamilial disorders with atrophic dermatosis, bilateral cataracts and endocrine features. Striking differences, however, are evident in the skin changes, as well as in the time and in the site of their occurrence. The difference in the appearance of the patient, especially in respect to the symptoms of presenility (progeria) justify separating Werner's and Rothmund's syndromes into two different but related clinical entities.

(14) Both syndromes may not develop in all their features and may occur as "forme fruste." Intimate acquaintance with the syndromes under discussion may facilitate their recognition even as forme fruste. Thus, more families stricken with these heredofamilial disorders will be discovered, bearing out my contention that the disorders are not so rare as now believed.

### ETIOLOGY

The survey of all cases demonstrates clearly that Werner's, as well as Rothmund's syndrome, is a recessive hereditary disorder. This conception cannot be altered by the occasional occurrence of cases with a normal family history. It is a special feature of these particular heredofamilial disorders that they occur collaterally in one generation. Werner, as well as Rothmund, suggested that we are dealing with a disorder of the ectodermal layer, since both skin and lens are derived from the ectoderm. Such a theory is not substantiated by the multiplicity of symptoms, involving blood vessels, subcutaneous fat tissue, muscles and endocrine glands, especially not since we know the symptom complex of a heredofamilial disorder involving only the ectodermal layer—"ectodermal dysplasia of the anhydrotic and hydrotic type," which is entirely different from the syndromes under discussion.

Such authors as Bloch and Stauffer favor a primary endocrine disorder which is reflected in the skin as an explanation of the pathogenesis of the syndromes. Oppenheimer and Kugel, who reported an autopsy of a case of Werner's syndrome, found the parathyroid hyperactive. The Hamilton-Schwartz test was positive during life. These authors were inclined to attribute an etiological significance to the hyperactivity of the parathyroids. Oppenheimer, however, in a personal communication, states that he no longer adheres to the opinion that the parathyroid gland is predominately involved.

It is not unusual that in chronic diseases of young individuals the functions of the endocrine glands are impaired. The physical development of the body, growth as well as sexual maturity, suffers if other organs, like heart, lungs or kidneys, are congenitally underdeveloped. This may be so in our syndromes. The endocrine dysfunction may then be secondary to the heredofamilial constitutional skin disorder.

The heredofamilial character of the syndromes under discussion, however, is indicative of a more basic nature of its pathogenesis. This points to a defective germ plasm which manifests its multiple defects at different periods of life. The multiple defects result in abiotrophic processes not only of organs which originate from the ectodermal layer, but also of organs which originate from the other germinal layers. The only certain fact bearing on the etiology of these syndromes is its heredofamilial nature. For this reason the occurrence of defects of the entire germinal plasm, recessive in heredity, seems the most plausible explanation of the pathogenesis of Werner's as well as Rothmund's syndrome.

### SUMMARY

1 The symptomatology of Werner's syndrome is established and demonstrated in cases from the literature and in four of our own. With the exception of Oppenheimer and Kugel's cases, the cases of Werner's syndrome in the literature are published under the misleading designation "Scleroderma and Cataracts."

2 The skin changes in Werner's syndrome are not those of true scleroderma. Because of its recessive heredofamilial occurrence it is suggested that the skin changes, as the other symptoms of Werner's syndrome, are the result of a defective germ plasm not manifesting itself until the second and third decades of life. A general term for the designation of the disorder as "progeria of the adult" is suggested since all symptoms of Werner's syndrome result in presenility of the patient.

3 The designation of the skin changes with a purely descriptive name, as "heredofamilial atrophic dermatosis with skin ulcers" seems more appropriate.

4 The skin ulcers in Werner's syndrome are not entirely trophic in origin since they appear only on exposed parts and are probably the result of pressure upon the thin, atrophic and stretched skin. The healing of the ulcers by grafting skin upon the skin defects supports such an opinion.

5 The symptomatology of Rothmund's syndrome is illustrated by cases selected from the literature and by a case of our own.

6 The skin changes of Rothmund's syndrome are classified in the literature as "poikiloderma" or "scleropoikiloderma." Such a classification does not accord with the heredofamilial occurrence of the skin disorder nor with the histological findings. In conformity with the designation of the skin disorder in Werner's syndrome it seems appropriate to use for the skin

changes in Rothmund's syndrome a simple descriptive name such as "heredo-familial atrophic dermatosis with telangiectases."

7 Both syndromes may occur as incomplete forms, so called "forme fruste."

8 The heredity in both forms is recessive. The collateral occurrence in brothers and sisters of one generation is often observed. Rothmund's syndrome starts usually in childhood, Werner's syndrome in the second and third decades.

9 Clinical syndromes related to Werner's and Rothmund's syndromes are discussed. A chart tabulating the features of Werner's and Rothmund's syndromes in comparison with related clinical entities is presented to aid in the differential diagnosis of these syndromes.

10 For the pathogenesis of Werner's syndrome and Rothmund's syndrome a purely ectodermal dysplasia as well as primary endocrine functional disturbance is rejected. The recessive heredity of both syndromes suggests as an explanation for its etiology the existence of multiple germ plasma defects manifesting themselves in abiotrophic features of various organs at different periods of life.

## BIBLIOGRAPHY

### I

- 1 WERNER, C. W. O. Über Katarakt in Verbindung mit Sclerodermie, Inaug. Dissert., Kiel, 1904.
- 2 VOSSIUS, A. Zwei Fälle von Katarakt in Verbindung mit Sclerodermie, Ztschr. f. Augenh., 1920, xliii, 640.
- 3 GUILLAIN, G., ALAJOUANINE, T., and MARQUEZY, R. Sclerodermie progressive avec cataracte double précoce chez un infantile, Bull. et mém. Soc. méd. d. hôp. de Paris, 1923, xxxix, 1489.
- 4 MANJUKOWA, N. Zur Frage über den Zusammenhang der Linsentrübungen mit Störungen der inneren Sekretion, Russk. Ophth. Jour. 2, Klin. Monatsbl. f. Augenh., 1923, lxv, 785.
- 5 PAPASTRATYAKIS, C. Un nouveau syndrome dystrophique juvénile, Paris méd., 1922, xlv, 475.
- 6 BARBOT, E. M. La sclerodermie associée à la cataracte, Thèse de Paris, 1925.
- 7 MONIER-VINARD, and BARBOT, E. M. Sclerodermie et cataracte, syndrome familial, Bull. et mém. Soc. méd. d. hôp. de Paris, 1928, lvi, 708.
- 8 BAU-PRUSSAK, S. La dégénérescence génito-sclérodermique, Rév. Neurol., 1926, Tome I, 316.
- 9 SAINTON, M., and MAMOU, H. Syndrome pluriglandulaire avec sclerodermie et cataracte, Bull. et mém. Soc. méd. d. hôp. de Paris, 1927, li, 1685-1690.
- 10 HASHIMOTO, T. Ein Fall von Sklerodermie kombiniert mit Katarakt, Zentralbl. f. Hautkrankh., 1930, xxxvii, 205.
- 11 EGUCHI, H. Über Cataracte bei pluriglandularem Infantilisismus mit Sklerodermie, Art. Soc. Ophth. Jap., 35, Ref. Zentralbl. f. d. ges. Ophth., 1931, xxv, 507.
- 12 SÉZARRY, A., FAVORY, A., and MAMOU, H. Syndrome tardif de sclerodermie avec cataracte, associé à des troubles endocriniens, Bull. et mém. Soc. méd. hôp. de Paris, 1930, xlvii, 358.

- 13 MANOU, H Sclerodermie et cataracte, maladie de Rothmund, Thèse de Paris, 1931
- 14 KREBS, E, HARTMANN, E, and THIEBAUT, F Un cas familial de syndrome de sclerodermie avec cataracte, troubles endocriniens et neurovegetatifs associés, *Rev Neurol*, 1930, 1, 606, 755, *Rev Neurol*, 1930, 11, 121
- 15 OPPENHEIMER, B S, and KUGEL, V H Werner's syndrome, a heredofamilial disorder with scleroderma, bilateral juvenile cataract, precocious graying of the hair and endocrine stigmatization, *Trans Assoc Am Phys*, 1934, xlix, 358
- 16 OPPENHEIMER, B S, and KUGEL, V H Werner's syndrome, report of the first necropsy and of findings in a new case, *Am Jr Med Sci*, 1941, ccii, 629
- 17 VARNEY, R F, KENYON, A T, and KOCH, F S Association of short stature, retarded sexual development and high urinary gonadotropin titers in women, *Jr Clin Endocrinol*, 1942, 11, 137
- 18 ALBRIGHT, F, SMITH, P H, and FRASER, R. A syndrome characterized by primary ovarian insufficiency and decreased stature, *Am Jr Med Sci*, 1942, cciv, 625
- 19 WILKINS, L, and FLEISCHMANN, W Ovarian agenesis, *Jr Clin Endocrinol*, 1944, iv, 357

## II

- 20 ROTHMUND, A Über Katarakt in Verbindung mit einer eigentümlichen Hautdegeneration, *Arch f Ophth*, 1868, xiv, 159
- 21 ORMSBY, O S, and MONTGOMERY, H Diseases of the skin, 1943, Lea and Febiger, Philadelphia, p 592
- 22 VÖRNER, H Über zirkumskripten kongenitalen Defekt (Aplasie) der Cutis und Subcutis, *Arch f Dermat u Syph*, 1903, lxvi, 407
- 23 NIEDEN, A Kataraktbildung bei telangiectatischer Ausdehnung der Kapillaren, *Centralbl f pract. Augenh*, 1887, 11, 353
- 24 TERRIEN, F, and PRÉLAT Telangiectasie généralisée et cataracte congenitale, *Soc Ped de Paris*, 1909, 11, 370
- 25 ZINSSER, F Atrophia cutis reticularis cum pigmentatione, *Ikonograph Dermat*, 1910, 5
- 26 JANOVSKY, V Drei Fälle familiärer Hautatrophie (Poikiloderma atrophicans), *Arch f Dermat*, 1921, cxix, 388
- 27 SIEGRIST, A Der graue Altersstar, 1928, Urban and Schwarzenberg, Berlin
- 28 SCHNYDER, A F Über Katarakt bei poikilodermie-artige Hauterkrankung, *Klin Monatsbl f Augenh*, 1924, xcii, 408
- 29 BLOCH, B, and STAUFFER, H Skin diseases of endocrine origin (dyshormonal dermatoses), poikiloderma-like changes in connection with underdevelopment of the sexual glands and dystrophia adiposogenitalis, *Arch f Dermat u Syph*, 1929, xix, 21
- 30 JACOBI, E Poikiloderma atrophicans vascularis, *Ikonograph Dermat*, 1908, Fasc 3, p 95-98
- 31 BOWMANN, K. M, and CLARK, E C A case of poikiloderma atrophicans vasculare, *Arch f Dermat u Syph*, 1927, xv, 583
- 32 WERTHEIM, L Atrophie der Hypophysis cerebri bei einem der Poikiloderma atrophicans vasculare nahestehendem Fall von Hautatrophie, *Arch f Dermat*, 1926, ci, 464
- 33 LEGINSKY, R Zur Pathogenese der Poikiloderma, *Dermat. Wchnschr*, 1927, lxxvii, 321
- 34 SEEFELDER, R Über familiäres Auftreten von Katarakt und Poikilodermie, *Ztschr f Augenh*, 1935, lxxxvi, 81
- 35 MARCHIONINI, A, and LUX, L Juvenile Katarakt bei Skleropoikilodermie, *Arch f Dermat u Syph*, 1937, clxxvi, 309
- 36 JAFFE, K Sklero-poikilodermie, *Arch f Dermat u Syph*, 1936, cli, 257
- 37 THANNHAUSER, S J Endocrine Organe und Gelenkerkrankungen Rheumprobleme II. 1931, Georg Thieme, Leipzig, p 161

## III

- 38 ANDOGSKY, N Cataracta dermatogenes, *Klin. Monats-bl f. Augenh*, 1914, lii, 824
- 39 VOGT, A. Weitere Ergebnisse der Spaltlampenmikroskopie, *Arch f Ophth.*, 1922, civ, 197.
- 40 LOWENSTEIN, A. Katarakt bei Neurodermitis, *Klin Monatsbl f. Augenh*, 1924, lxxii, 653, 1926, lxxvi, 539
- 41 OELENDORF, H, and LEVY, G Neurodermitis und Katarakt, *Arch f. Dermat*, 1932, clxiv, 683
- 42 MITZGER, E Katarakt bei Neurodermitis, *Klin Monats-bl f Augenh*, 1932, lxxix, 821
- 43 LASLÓ, G Neurodermitis und Katarakt, *Klin Monatsbl f. Augenh*, 1933, xci, 133
- 44 KUGLIDRIG, I Juvenile Katarakt bei Dermatosen. Cataracta syndermatotica, *Klin Monatsbl. f Augenh*, 1934, xcii, 484
- 45 OLTSMANN, H. J Cataracta dermatogenes, *Zentralbl f d ges Ophth*, 1932, xxviii, 90
- 46 FRANCESCHETTI, A Die Vererbung von Augenleiden (Scheek-Bruckner), 1930, Bd 1, S 631
- 47 FRANCISCHETTI, A Über Katarakt bei Hautleiden, *Ztschr f Augenh*, 1934, lxxiv, 184
- 48 HUTCHINSON, J Congenital absence of hair and mammary glands, etc, *Medicochir Trans*, 1886, lxi, 473.
- 49 GILFORD, H On a condition of mixed premature and immature development, *Medicochir Trans*, 1897, lxx, 17.
- 50 GILFORD, H Progeria a form of senilism, *Practitioner*, 1904, lxxiii, 188
- 51 GILFORD, H. Progeria and ateliosis, *Lancet*, 1913, i, 412
- 52 CURTIN, V. T, and KOTZEN, H F. Progeria, *Am Jr Dis Child*, 1929, xxxviii, 993
- 53 MITCHELL, E C, and GOLTMANN, D W Progeria, report of a classic case with a review of the literature since 1929, *Am Jr Dis Child*, 1940, lix, 379
- 54 MANSCHOT, W A Een geval van progeria-nanie (Progeria von Gilford), *Nederl tijdschr geneesk*, 1940, lxxiv, 3374
- 55 ORRICO, J, and STRADA, F Anatomico-clinical study of a case of senile dwarfism (progeria), *Arch de méd d enf*, 1927, xxx, 385
- 56 HOFFMAN, I Zur Lehre von der Thomson'schen Krankheit mit besonderer Berücksichtigung des dabei vorkommenden Muskelschwundes, *Deutsch Ztschr f Nerven*, 1900, xviii, 198
- 57 STEINERT, H Atrophische Myotonic, *Deutsch Ztschr f Nerven*, 1909, xxxvii, 58
- 58 CURSCHMANN, H Über familiäre atrophische Myotonic, *Deutsch Ztschr f Nerven*, 1912, xlv, 161
- 59 HAUPTMANN, A Die atrophische Myotonic, *Deutsch Ztschr f Nerven*, 1916, lv, 53
- 60 NAEGELI, O Über Myotonia atrophica, speziell über die Symptome und die Pathogenese der Krankheit, *München med Wchnschr*, 1917, lxi, 1631
- 61 ROHRER, K. Über Myotonia atrophica, *Deutsch Ztschr f Nerven*, 1916, lv, 242
- 62 MCKAY, W, and DAVIDSON, A M Congenital ectodermal defect, *Brit. Jr Dermat*, 1929, xlix, 1
- 63 THANNHAUSER, S J Hereditary ectodermal dysplasia of the "anhidrotic type," *Jr Am Med Assoc*, 1936, cvi, 908
- 64 THANNHAUSER, S J Hereditary ectodermal dysplasia of the anhidrotic and hydrotic types, *Practitioner Library of Med and Surg*, 1938, Appleton-Century Co, New York, xiii, 473

# ABSORPTION AND EXCRETION OF IRON\*

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CONSIDERING the importance of iron in the body and the extensive work that has been done on this subject, still relatively little is known concerning metabolism of iron. During most of the last century many extensive arguments were carried on as to whether or not iron was absorbed at all. The misconception that it was not absorbed arose from the fact that the small amounts of iron in the body could not be detected by chemical methods available at the time. As late as 1893, Stockman<sup>1</sup> felt it necessary to refute the theory, which was apparently current then, that the action of iron in chlorosis arose from the precipitation of poisonous hydrogen sulfide in the intestine. This he did satisfactorily by successfully treating patients who had chlorosis with subcutaneous injections of citrate of iron. During the first part of this century, mainly under the influence of the histologic school, a theory of metabolism of iron was evolved which has more or less continued to be in vogue. The most widely accepted current theory has been succinctly stated in Starling's "Human Physiology"<sup>2</sup> "The absorption of iron takes place in the duodenum and upper part of the jejunum. Only 1 or 2 mg appear in the urine, all the rest being excreted in the large gut and appearing in the feces, chiefly as sulfide of iron." In other words, this view assumes that iron is absorbed from the upper part of the intestine regardless of stores in the body. The excess is then secreted by a specific action of the colonic mucosa.

Before the present work was undertaken, reports of the previous investigations were thoroughly surveyed and references to them are given in the thesis which forms the basis of this paper. The main purpose here, however, is to report any contribution we ourselves may be able to make on the subject.

## RATIONALE AND GENERAL METHOD OF PRESENT WORK

The work reviewed seemed to show fairly definitely that iron is not excreted by the dog. However, investigations based on human subjects are open to criticism from three points. First, in experiments that necessitate administration of iron by mouth, the difficulty is encountered of determining

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From the Mayo Foundation (Fellow in Surgery, Dr. Little) (Division of Biochemistry, Dr. Power) and Mayo Clinic (Division of Medicine, Dr. Wakefield). Since this paper was written Dr. Little has entered the army and is now an officer of the Medical Corps, Army of the United States.



many grams of iron in a large volume of stool with accuracy within a few milligrams. Second, after administration of iron by mouth two to four weeks are required for the intestine completely to eliminate the dose, as most of it is precipitated as iron sulfide, which tends to adhere to the mucosa and is passed slowly. Third, with the administration of iron by mouth, the additional variable factor of absorption, which is impossible of determination and control, must be considered.

In the present work we have tried to circumvent these difficulties by intravenous administration of the iron. In this way it is possible to be sure of the amount of iron that reaches the interior of the body and large quantities do not have to be determined in the stools over long periods of time. In general, the iron in the feces was determined during three successive periods. The first and third periods were used as controls and, during the second period, iron was injected intravenously. This sequence does not apply to the study reported as third in this paper and summarized in table 3, which will be referred to again later.

#### DETAILS OF PROCEDURE

The metabolic processes of the three subjects used apparently were satisfactory. They had been in an institution for several months on an adequate diet and could be assumed to have ingested adequate quantities of iron. Their stools were repeatedly negative for blood by the benzidine test. During the entire time of the study they were kept in a hospital ward where they could be observed. During the test periods they were placed on diets of approximately constant daily content of iron, as calculated from accepted analyses. Urine and stools were collected separately by means of a special, nonferrous bifurcated commode, stools were separated into periods by means of carmine markers. The receptacles were two glass containers which previously had been rinsed with diluted hydrochloric acid. Collections of blood were made from veins of the arm, with a stainless steel 18 gauge needle. To prevent hemolysis, a tourniquet or a syringe was not used. The first 10 c c of blood were allowed to flow into a tube that contained heparin and were used to ascertain the value for hemoglobin, the number of erythrocytes per cubic millimeter and hematocrit values. The next 10 c c were collected under oil for determinations of serum iron.

The iron was administered as ferrous ascorbate. This compound was first described by Szent-Gyorgyi<sup>3</sup> and has been used fairly extensively by Heilmeyer,<sup>4</sup> by Fleischhacker and Schurer-Waldheim<sup>5</sup> and by Friend<sup>6</sup>. This compound was chosen because it can be safely administered in sufficient quantities. Our supply of ferrous ascorbate was prepared by us after the method of Maurer and Schiedt.<sup>7</sup> Each preparation was analyzed for content of iron and was kept in a desiccator. At the time of use a quantity was weighed which would contain the desired amount of iron. This was dissolved in 200 to 300 c c of physiologic saline solution and was immediately

injected The injections contained 30 to 40 mg of iron each and were given in a period of 45 to 75 minutes Faster administration caused mild symptoms, characterized by warmth and flushing of the face There were no late symptoms and only one episode of thrombosis The thrombosis followed several injections into the same vein

### ANALYTIC PROCEDURE

Determination of iron in blood serum was accomplished by a modification of the procedure described by Moore<sup>8</sup> The modified procedure was as follows

*Ashing* Five (or 10) c c of serum were measured into a 100 c c Kjeldahl flask, followed by 5 (or 10) c c of concentrated nitric acid and two glass beads The mixture was heated by means of a microburner over wire gauze, gently at first, then somewhat more vigorously so that the volume was reduced to 2 to 3 c c during about 30 minutes The flask was allowed to cool for one to two minutes, then 2 c c of 70 per cent perchloric acid were added, and the heating over wire gauze was continued with the flame adjusted so that the nitric acid remaining in the digest was distilled off in about 15 to 20 minutes With the appearance of the white fumes of perchloric acid, which indicated that the major part of organic matter had been destroyed, the heat was increased and the solution was heated vigorously over the free flame for 30 to 40 minutes longer to remove all traces of yellow or green color The digest was then allowed to cool, the sides of the flask were rinsed down with 3 to 4 c c of iron-free distilled water, and the mixture was boiled until the added water was distilled off, then the mixture was heated more vigorously for another 15 to 20 minutes The digest was again cooled, 10 c c of distilled water were added, and the mixture was boiled for one to two minutes The flask was then removed from the flame, a drop of concentrated nitric acid was added to the hot solution, followed by 10 c c more of distilled water Known amounts of iron to serve as standards for colorimetric comparison, 5 or 10 gamma in each sample, were carried through the above procedure, with the same amounts of the various reagents

*Development of Color* To each unknown and standard, prepared as has been described, were added 6 c c of iso-amyl alcohol and 3 c c of 20 per cent solution of sodium thiocyanate (The flasks containing the solutions were cooled somewhat below room temperature before the addition of the alcohol ) After the red iron sulfocyanate complex had been extracted into the alcohol layer, by shaking the flasks for two to three minutes, the colored layers were pipetted off directly into 20 mm absorption cells for determination of light absorption by means of the Pulfrich photometer, or into the small test tubes used with the Klett-Summerson photo-electric colorimeter With the latter instrument, the green filter number 54, with maximal light transmission at wave length 540 mm, was used

*Determination of Iron in Feces* The total amount of feces collected in each period was treated with four 50 c.c. portions of concentrated nitric acid for several days, until the mixture was homogeneous, after which aliquots of 25 to 30 gm were weighed into Kjeldahl flasks of a capacity of 300 c.c. These samples were then ashed with nitric and perchloric acids, and the iron thiocyanate color complex was developed, extracted and determined essentially as described for serum.

## RESULTS

Table 1 shows the results obtained with the first subject. This was a man, 46 years of age, afflicted with syphilis of the central nervous system but otherwise in good health. The total time of study consisted of 26 consecutive days which were divided into three periods of nine, ten and seven days respectively. During the second period a total of 311 mg of iron was administered intravenously in eight injections.

TABLE I

A Man, 46 Years of Age, Who Had Syphilis of the Central Nervous System Iron Administered Intravenously during Second Period Patient on Constant Diet during Test

|   |                  | Period 1<br>9 days | Period 2<br>10 days | Period 3<br>7 days |
|---|------------------|--------------------|---------------------|--------------------|
| Iron, gamma per 100 c.c. serum          | Begin            | 216                | 186                 | 145                |
|   | End              | 186                | 145                 | 232                |
| Hemoglobin, gm per 100 c.c. blood       | Begin            | 13.5               | 13.5                | 13.5               |
|   | End              | 13.5               | 13.5                | 13.5               |
| Erythrocytes, millions per cu mm blood  | Begin            | 3.99               |                     | 4.34               |
|   | End              |                    | 4.34                | 4.35               |
| Volume packed erythrocytes (hematocrit) | Begin            | 43.4               |                     | 43.9               |
|   | End              |                    | 43.9                | 46.8               |
| Iron given in period, mg                |                  | 0                  | 311                 | 0                  |
| Iron in urine, mg                       | Total for period | 0.41               | 7.01                |                    |
|   | Daily average    | 0.04               | 0.70                |                    |
| Iron in stools, mg                      | Total for period | 159.0              | 152.2               | 109.3              |
|   | Daily average    | 17.7               | 15.2                | 15.6               |

The concentration of hemoglobin, the erythrocyte count and the volume of packed erythrocytes remained approximately constant during the study. The small variations in the last two might possibly be due to the fact that the determinations were made on heparinized blood several hours after collection. The value for serum iron was somewhat high, varying from 145

to 232 gamma per 100 c c During the period of study the value did not change significantly, however The iron in the urine during the first control period totaled 0.41 mg, or an average of 0.04 mg daily This increased during the period of administration of iron to a total of 7.01 mg, or a daily average of 0.70 mg The daily fecal iron remained essentially constant during the three periods, being 17.7 mg, 15.2 mg and 15.6 mg, respectively

TABLE II

A Man, 36 Years of Age, Who Had Syphilis of the Central Nervous System  
Iron Administered Intravenously during Second Period  
Patient on Constant Diet during Test

|  |                  | Period 1<br>4 days | Period 2<br>8 days | Period 3<br>5 days |
|--|------------------|--------------------|--------------------|--------------------|
| Iron, gamma per 100 c c<br>serum           | Begin            | 115                | 86                 |                    |
|  | End              | 86                 | 46                 |                    |
| Hemoglobin, gm per 100 c c<br>blood        | Begin            | 11.4               | 11.6               |                    |
|  | End              | 11.6               | 10.8               |                    |
| Volume packed erythrocytes<br>(hematocrit) | Begin            | 40.5               | 41.8               |                    |
|  | End              | 41.8               | 35.6               |                    |
| Iron given in period, mg                   |                  | 0                  | 156                | 0                  |
| Iron in stools, mg                         | Total for period | 26.6               | 48.9               | 32.6               |
|  | Daily average    | 6.6                | 6.1                | 6.5                |

Table 2 shows the results noted in a study of a paretic man 36 years of age He was followed during 17 consecutive days, divided into three periods of four, eight and five days each During the second period he was given 156 mg of iron in four injections

The concentration of hemoglobin and volume of packed erythrocytes remained essentially constant The values for serum iron were somewhat

TABLE III

A Man, 40 Years of Age, Who Had Schizophrenia 30 mg of Iron Administered Intravenously  
Injection Started at 7:15 a m and Concluded at 7:45 a m

|  | Volume Urine<br>c c | Total Iron Excreted<br>mg | Average Excretion<br>per Hour mg |
|--|---------------------|---------------------------|----------------------------------|
| Period 1—1 hour, 30 minutes<br>(7:15 a m to 8:45 a m)  | 175                 | 0.19                      | 0.13                             |
| Period 2—4 hours, 45 minutes<br>(8:45 a m to 1:30 p m) | 200                 | 0.06                      | 0.01                             |
| Period 3—3 hours, 30 minutes<br>(1:30 p m to 5 p m)    | 200                 | 0.03                      | 0.01                             |

Total excretion in approximately 10 hours, 0.29 mg

low, varying from 46 to 115 gamma per 100 c.c. The accuracy of the 46 gamma is probably questionable. The average daily fecal iron remained fairly constant, being 6.6 mg, 6.1 mg and 6.5 mg for the respective periods.

Table 3 shows the results obtained from further study of urinary excretion following intravenous injection. The subject was a man, 40 years of age, who was suffering from schizophrenia. Iron, 30 mg, was given intravenously and the urine was collected at intervals during the following approximately 10 hours. The total excretion during this period was only 0.29 mg, 0.19 mg of which appeared during the first 90 minutes.

### SUMMARY AND COMMENT

Determination was made of the amount of iron in the feces of two men whose iron reserve apparently was normal. Injection of relatively large amounts of iron by vein caused no detectable increase in the fecal iron. This conclusion is in agreement with the results obtained in dogs by Henriques and Roland,<sup>9</sup> Hahn and associates<sup>10, 11, 12</sup> and Quinke.<sup>13</sup> It would tend to lend confirmation to the hypothesis advanced by McCance and Widdowson<sup>14, 15</sup> that the body has no mechanism whereby an excess of iron can be excreted. Over a control period of nine days one of these two men was found to excrete approximately 0.045 mg of iron per day in his urine. This is somewhat lower than the determinations of Farrar and Goldhamer<sup>16</sup> who found 0.02 mg per 100 c.c. and those of Henriques and Roland who estimated 0.08 to 0.32 mg per day.

As found in study of a third man, following intravenous injection of iron there is a marked increase in the amount of urinary iron. This has been found by other observers. The total amount was relatively small, however, being only 0.29 mg within 10 hours following the injection of 30 mg. More than 65 per cent of this appeared within the first 90 minutes. This increased excretion is apparently due to the sudden and marked increase of iron in the blood and probably does not take place following its normal absorption from the intestine.

We are aware that, at postmortem examination in cases of general paralysis of the insane, pigment is found in the brain. This pigment is known to be iron and is associated with the local degenerative changes. We do not believe that this deposition substantially disturbs the systemic metabolism of iron. Nevertheless, the phenomenon should be mentioned here for its possible significance as knowledge is extended.

### BIBLIOGRAPHY

- 1 STOCKMAN, RALPH. The treatment of chlorosis by iron and some other drugs, *Brit Med J.*, 1893, 1, 881-885, 942-944.
- 2 STARLING, E. H. Human physiology, Ed 6, 1933, Lea and Febiger, Philadelphia, 1122 pp.
- 3 SZENT-GYORGYI, A. Eine Farbenreaktion der Ascorbinsäure, *Ztschr f physiol Chem*, 1934, CCXXV, 168.

- 4 HEILMEYER, L Die Behandlung eisenempfindlicher Anamien mit askorbinsäurem Eisen, zugleich ein Beitrag zum Mechanismus der Eisenwirkung und zur Frage der Eisenmangelkrankheit, *Deutsch Arch f klin Med*, 1936, clxxix, 216-231
- 5 FLEISCHACKER, H, and SCHURER-WALDHEIM, F Zur peroralen und intravenösen Therapie mit ascorbinsäurem Eisen, *Wien klin Wchnschr*, 1938, li, 776-780
- 6 FRIEND, D G Iron ascorbate in the treatment of anemia, *New England Jr Med*, 1938, ccxiv, 910-912
- 7 MAURER, KURT, and SCHIEDT, BRUNO Das Verhalten der d-Arabsäure und des Vitamins C gegenüber Ferrosalzen, *Biochem Ztschr*, 1936, cclxxxv, 67
- 8 MOORE, C V Studies in iron transportation and metabolism, chemical methods and normal values for plasma iron and "easily split-off" blood iron, *Jr Clin Invest*, 1937, xvi, 613-626
- 9 HENRIQUES, V, and ROLAND, H Zur Frage des Eisenstoffwechsels, *Biochem Ztschr*, 1928, cci, 479-485
- 10 HAHN, P F, and WHIPPLE, G H Radioactive iron and its metabolism in anemia, *Jr Am Med Assoc*, 1938, cxi, 2285-2286
- 11 HAHN, P F, BALE, W F, LAWRENCE, E O, and WHIPPLE, G H Radioactive iron and its metabolism in anemia, *Jr Exper Med*, 1939, lxi, 739-753
- 12 HAHN, P F, BALE, W F, HETTIG, R A, KAMEN, M D, and WHIPPLE, G H Radioactive iron and its excretion in urine, bile and feces, *Jr Exper Med*, 1939, lxi, 443-451
- 13 QUINKE Quoted by GOTTLIEB, R Ueber die Ausscheidungsverhältnisse des Eisens, *Ztschr f physiol Chem*, 1891, xv, 371-386
- 14 McCANCE, R A, and WIDDOWSON, E M Fate of elements removed from blood-stream during treatment of polycythaemia by acetyl-phenylhydrazine, *Quart. Jr Med*, 1937, vi, 277-286
- 15 McCANCE, R A, and WIDDOWSON, E M Absorption and excretion of iron, *Lancet*, 1937, ii, 680-684
- 16 FARRAR, G E, and GOLDHAMER, S M The iron requirement of the normal human adult, *Jr Nutr*, 1935, x, 241-254

# VENTRICULAR TACHYCARDIA—A REPORT OF TEN CASES, EIGHT OF WHICH WERE TREATED WITH QUINIDINE WITH RECOVERY IN SEVEN<sup>1</sup>

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REVIEW of the recent literature reveals little dealing with the effects of large doses of quinidine on ventricular tachycardia. No series comparable in size to this one has been noted within the past 15 years. McMillan<sup>1</sup> recently reported two cases following coronary thrombosis treated successfully with quinidine. Reich<sup>2</sup> reported a cure with a total of 185 grams given in a period of two and a half days, a dosage believed by him and also by Levine<sup>3</sup> and Gold<sup>4</sup> to be the largest dose given in a period of 60 hours. Some of the cases in this series had quinidine in doses approaching the amount given by Reich, with a favorable outcome. In Reich's case a QRS interval greater than 0.18 second was avoided for fear of producing ventricular fibrillation. It is not believed that the QRS duration as influenced by quinidine should be used as an index of quinidine poisoning in the therapy of this arrhythmia. In some of the cases of this series the gradual spread of the QRS interval well exceeded the arbitrary limit of 0.18 second with no observable detrimental effect—indeed the lengthening of the interval was a probable factor in the termination of the arrhythmia. It was invariably associated with a slowing of the ventricular rate and often with a feeling of well being.

Levine and Fulton<sup>5</sup> gave as much as 112 grams of quinidine in 24 hours to a patient with ventricular tachycardia. Viko, Marvin and White<sup>6</sup> gave daily doses up to 60 grams. In recent years the trend has been to exceed by far the recommended dose of 15 to 30 grains daily. Levine has recently recommended large doses e.g., 15 grains every four hours in the treatment of ventricular tachycardia complicating coronary thrombosis. Fishberg<sup>7</sup> states that he has failed to abolish the rhythm in two cases following coronary thrombosis "perhaps because the maximum dose recommended by him (Levine) was not given."

Williams and Ellis<sup>8</sup> did not evaluate the results of quinidine therapy in the 36 cases from the files of the Boston City Hospital because of the lack of uniformity in the treatment of this arrhythmia and also because the dosage administered was much too low. They stated that in "certain individual cases the value of the drug seems unquestioned. Even if the drug

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does not abolish the attack, a slowing of the rate often occurs and produces improvement in the circulation "

Woodruff<sup>9</sup> feels that quinidine is absolutely indicated in ventricular tachycardia. He also is of the opinion that treatment should be started early and that the dose of quinidine should be large. He mentions the prophylactic administration in cases of coronary thrombosis, so often stressed by Levine. He discusses the method of administration proposed by White using six grain doses every two hours for five doses during the day and repeating as often as is necessary until a normal sinus mechanism is restored. He states that larger doses may sometimes be required.

Stempien and Katz<sup>10</sup> reported a case of this arrhythmia successfully treated with quinidine augmented with potassium. These authors are of the opinion that quinidine "is by far the most reliable drug in the treatment of paroxysmal ventricular tachycardia." They are quite impressed with the favorable result in the therapy of this case, and attribute a large measure of the success to the simultaneous use of the potassium. It may be stated at this point that atropine has also been suggested as an adjunct by Levine. We have had insufficient experience to attempt any evaluation of these secondary drugs in the treatment of this ectopic rhythm.

With respect to Levine's suggestion as to the use of quinidine following coronary thrombosis in the anticipation of the arrhythmias, Master feels that the administration of this drug is dangerous in the acute stages. Furthermore he feels that its evaluation in the acute stages is fraught with uncertainty in view of the relatively transitory nature of the arrhythmias in this condition. Comeau<sup>11</sup> feels that quinidine is the drug of choice in the treatment of ventricular tachycardia.

Kerr is not enthusiastic about the use of quinidine in the control of ventricular tachycardia. He feels that the paroxysms are transient in nature and that conclusions are drawn only with great difficulty. However, it seems to the writer that the close relationship between the administration of the drug and the favorable outcome in a great number of the reported cases, and in the cases of this series, is too obvious to indicate anything other than a causal effect in the termination of the arrhythmia. It must also be stated that no untoward effect was noted in this series, the rhythm having been successfully terminated in seven of the eight treated cases.

A word must be included at this time with respect to the usage of quinidine. In accordance with the Government's policy regulating the use of this critical drug, its administration has been restricted to attacks of ventricular tachycardia, to coronary thromboses complicated by frequent extrasystoles, and to prolonged attacks of paroxysmal supraventricular tachycardia uncontrolled by the usual methods, including the use of mecloyl. The administration of the drug is closely supervised by the cardiac service. Perhaps, on occasion, we have exceeded the maximum allowable dose but it was only because we honestly felt that it would have a life saving effect.



The 10 cases reported here have been observed within a period of four years, the high incidence no doubt resulting from the type of patient seen in this 600-bed general hospital. The patient load is practically entirely male and the average age of veterans of World War I today is slightly over 51 years. It is thus seen that an opportunity is provided for the study of a selected group of patients of an appropriate sex and age with respect to the degenerative vascular lesions. Ample facilities exist for detailed cardiovascular studies.

### CASE REPORTS

*Case 1* A 50 year old white lawyer had known cardiac disease with anginal syndrome since December 1943. There was no history of a previous coronary thrombosis and he had never shown signs of a failing myocardium other than the angina of effort which was of mild to moderate severity. He was not a known hypertensive. At 8 45 p.m. on October 14, 1944, he was admitted in an apparently terminal state with the history of the onset of severe oppressive retrosternal pain at about 5 p.m. on that day. At the time of admission he was cyanotic and in shock. The pulse was imperceptible and no blood pressure reading was obtainable. The ventricular rate was 140 and apparently regular. (He was not seen by the author.) There was an apical gallop present, no friction rub was heard. Electrocardiogram showed a ventricular tachycardia. He died at 8 05 a.m., October 15, 1944.

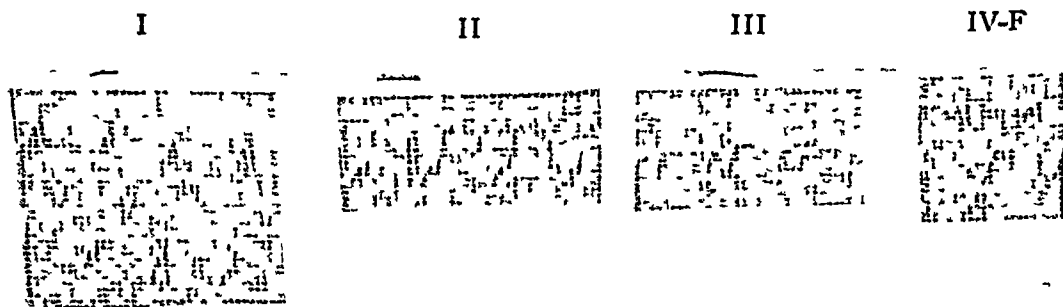


FIG 1 *Case 1* This was the presenting tracing on a patient who died promptly after admission. He received no quinidine. Clinically he presented findings suggesting a massive infarction. Postmortem examination revealed a large hemorrhagic infarction of the anterolateral wall of the left ventricle.

*Summary* A 50 year old white male, with known anginal syndrome, was admitted with an acute myocardial infarction complicated by a ventricular tachycardia. He appeared in a terminal state at the time of admission and received sedation and intravenous aminophyllin with no favorable effect. He was not seen in consultation and received no quinidine. Postmortem examination revealed extensive coronary artery disease of the atherosclerotic type. The left circumflex branch was the only vessel which showed some degree of patency. There was a fresh thrombus in the anterior descending branch of the left coronary artery with a fairly large area of hemorrhagic infarction of the anterolateral portion of the left ventricle. There were marked fibrotic changes throughout the entire myocardium of the left ventricle.

*Case 2* A 48 year old farmer was admitted October 5, 1942, because of genitourinary difficulty, including hematuria and the passage of gravel. A day prior to admission he had pain in the right costovertebral region. He had suffered with precordial pain associated with exertion for a number of years, but his electrocardiogram had always been within normal limits. He was a known hypertensive, but his heart

| Case No | Age | Digitalis            | Underlying Heart Disease                                 | Hypertension | Quinidine Dosage until Cessation of Arrhythmia | Ventricular Rate at Onset | QRS Interval | Congestive Failure | Total Duration of Attack | Anginal Syndrome | Toxicity              | Remarks   |
|---------|-----|----------------------|--|--------------|--|---------------------------|--------------|--------------------|--------------------------|------------------|-----------------------|---|
| I       | 50  | No                   | Anterior wall infarction                                 | No           | Untreated                                      | 180                       | 0 17         | No                 | Unknown                  | Yes              | None                  |   |
| II      | 48  | No                   | None demonstrated  | Yes          | Untreated                                      | 200                       | 0 14         | No                 | Less than 24 hours       | No               | None                  | T wave inversion  |
| III     | 47  | No                   | Anterior wall infarction                                 | Yes          | 114 grains in 55 hours                         | 170                       | 0 11         | Yes                | 55 hours                 | No               | None                  | Coupling due to ventricular premature contraction       |
| IV      | 49  | No                   | Posterior wall infarction                                | Yes          | 24 grains in 24 hours                          | 125                       | 0 12         | No                 | Less than 24 hours       | Yes              | None                  | 2 1 AV block  |
| V       | 46  | No                   | Anterior wall infarction                                 | No           | 120 grains in 4½ days                          | 160                       | 0 18         | No                 | 4½ days                  | No               | None                  |   |
| VI      | 51  | Yes 8 cu in 4 days   | Anterior wall infarction                                 | Yes          | 48 grains in 12 hours                          | 200                       | ?            | Yes (Left sided)   | 12 hours                 | No               | None                  | Died  |
| VII     | 59  | Yes after vent tachy | Coronary arteriosclerosis and hypertension heart disease | Yes          | 525 grains in 9 days                           | 200                       | 0 13         | Yes                | 9 days                   | No               | Diarrhea and vomiting | AV Dissociation<br>→ Nodal rhythm<br>→ Reg sinus rhythm |
| VIII    | 60  | Yes after vent tachy | Coronary arteriosclerosis and hypertension heart disease | Yes          | 72 grains in 2 days                            | 200                       | 0 13         | Yes                | 14-16 days               | No               | Diarrhea and vomiting | AV Dissociation<br>→ Reg sinus rhythm                   |
| IX      | 16  | No                   | Coronary disease   | No           | 174 grains in 3 days                           | 216                       | 0 16         | No                 | 6 days                   | No               | None                  | T wave inversion  |
| X       | 51  | No                   | Coronary arteriosclerosis and hypertension heart disease | No           | 24 grains in 7 hours                           | 182                       | 0 16         | No                 | 7 hours                  | No               | None                  | AF—Lead I<br>RSR—Lead II<br>Vent tachy<br>Lead III      |

was not enlarged. There were no complaints with reference to his cardiovascular system at the time of admission.

His ventricular rate was 200 per minute and regular, not being altered by carotid sinus pressure. The blood pressure was 112 mm Hg systolic and 96 mm. diastolic, the heart was within normal limits as to size. There was no evidence of congestive heart failure. There was some peripheral and retinal sclerosis.

Electrocardiogram revealed a ventricular tachycardia. He was sedated with morphine and placed on quinidine in doses of three grains four times daily. However, the tachycardia ceased spontaneously prior to the administration of the drug, having persisted for less than 24 hours. There was no clinical or electrocardiographic evidence of myocardial infarction, although at one time a left lateral wall infarct was hypothesized.

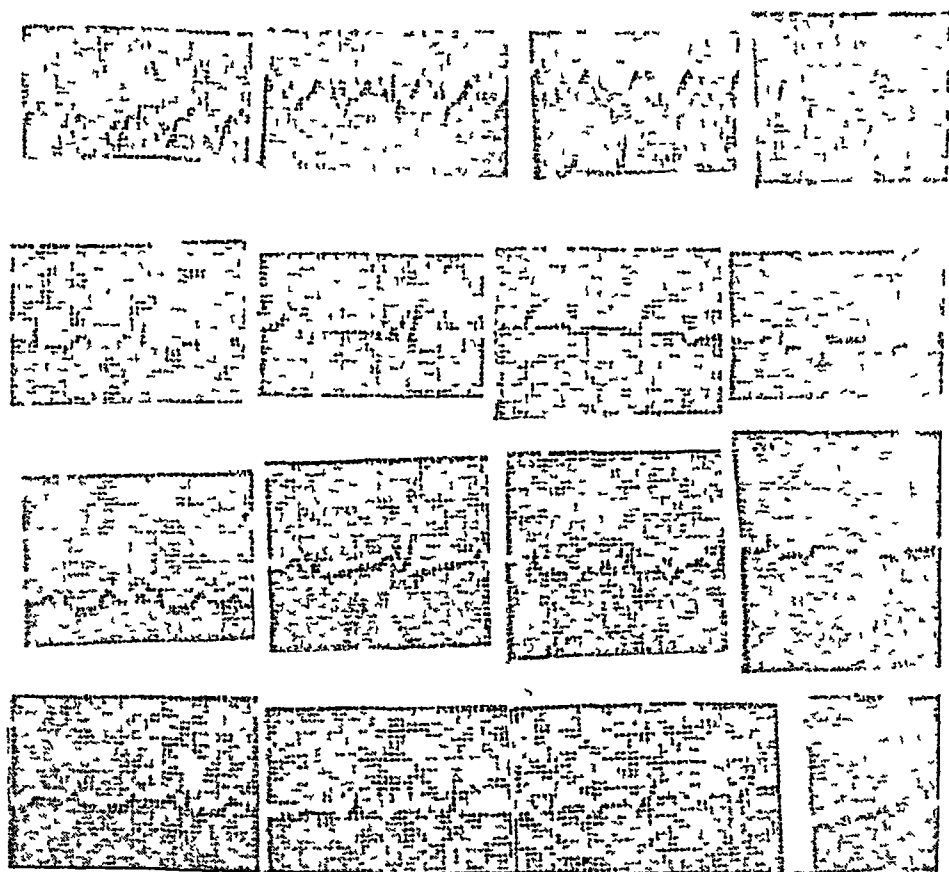


FIG 2 Case 2 Ventricular tachycardia, rate about 200 per minute. Note the very unusual and rather persistent T-wave changes in Lead IV-F and to a lesser degree in Lead I. These changes occurred in the absence of quinidine administration and tended toward reversal in a period of nine days. (From the author's case published in the *Journal of Laboratory and Clinical Medicine*, June 1944.)

**Comment** This case reveals the spontaneous termination of the arrhythmia under sedation. It is interesting in that it exhibited rather persistent T-wave inversion in Lead IV-F, and lesser changes in Lead I following the paroxysm. These changes reverted toward normal in a period of nine days. It shows that persistent wave inversion in multiple leads following bouts of tachycardia may occur and are not necessarily of ominous prognostic import. This case was reported in greater detail.<sup>12</sup>

**Case 3** A 47 year old white farmer was admitted December 22, 1943, in a condition which did not permit adequate anamnesis. He was a known hypertensive and

admitted increasingly severe exertional dyspnea over a period of three years prior to admission which finally necessitated bed rest three weeks immediately preceding admission. Examination revealed an acutely ill white male, dyspneic, and orthopneic. The neck veins were distended, the heart was enlarged, and the liver was palpated two centimeters below the right costal cage. The heart sounds were poor,  $A_2$  was ac-

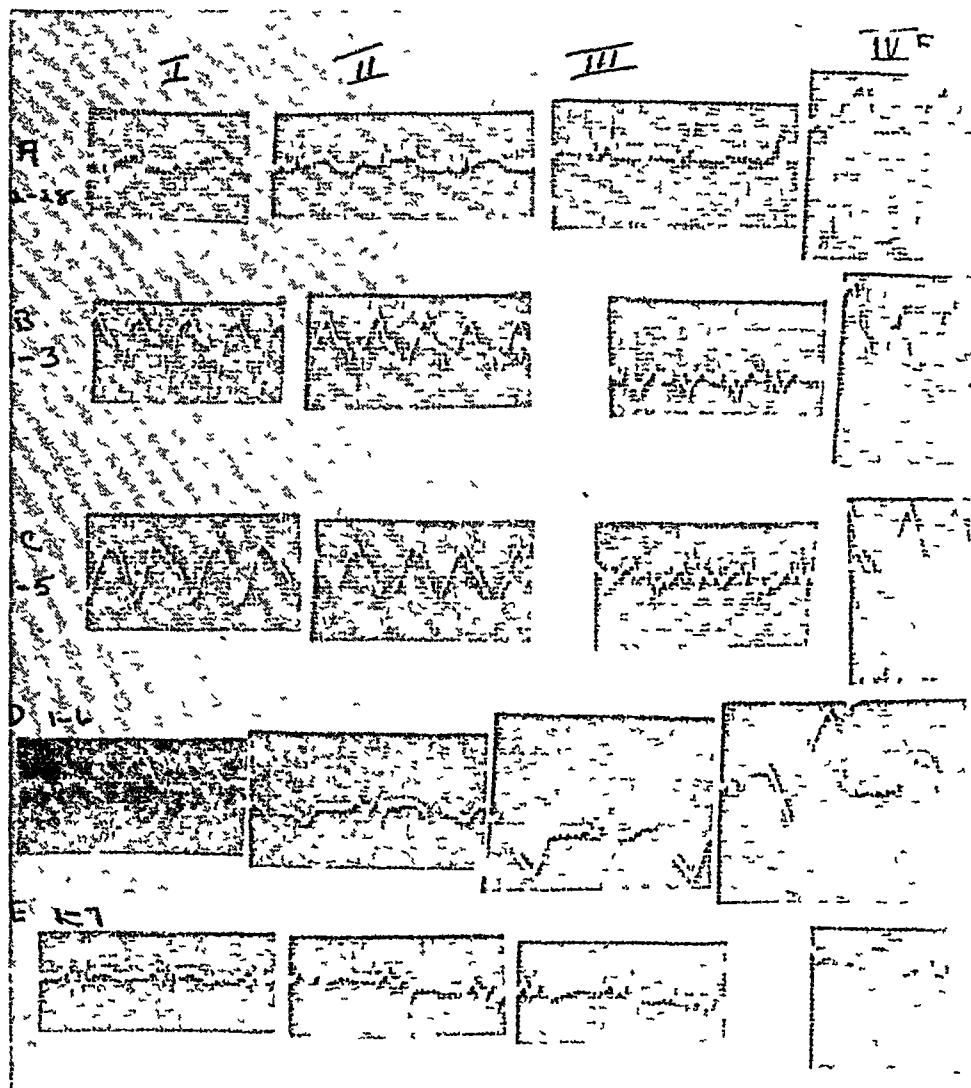


FIG 3 Case 3 These tracings represent an anterior wall infarction complicated by a ventricular tachycardia. The gradual widening of the QRS complexes and the replacement of the ventricular rhythm by a sinus mechanism with coupling are the interesting features of this series.

centuated and the blood pressure was 176 mm Hg systolic and 114 mm diastolic. There were dullness and medium sized moist râles over the right base posteriorly.

A diagnosis was made of hypertensive and coronary arteriosclerotic heart disease with congestive failure and hypostatic pneumonia, right lower lobe. The temperature reached  $102.4^{\circ}\text{F}$ . The pulse rate rose to 130 on the day following admission and then both slowly returned toward normal over a period of 10 days. The white blood cell count was 18,000, with 86 per cent polymorphonuclear leukocytes. He was placed

on sulfadiazine and showed slight but definite improvement. However, the heart sounds continued to be extremely poor. On December 28 the patient was able to give a more detailed history and it was ascertained that he had moderately severe retrosternal pain immediately prior to admission. With this information and in view of his clinical course, it was believed that the patient probably had a myocardial infarction. This contention was supported by the electrocardiogram (A) which revealed an anterior wall infarction.

He continued critically ill with an ashen gray cyanosis, relatively afebrile, and with a pulse rate ranging between 80 and 100 per minute until 8 45 a.m. January 3, 1944, at which time his ventricular rate was 170 per minute and quite regular. It did not respond to carotid sinus or ocular pressure. The blood pressure fell precipitously. The clinical impression of ventricular tachycardia was confirmed by electrocardiography (B).

He was given three grains of quinidine immediately and 12 grains three hours later, followed by six grains at four hour intervals. He appeared in extremis. On January 4 the rate was essentially unchanged and the quinidine was increased to nine grains every three hours day and night. This was augmented with potassium chloride, grains 15, three times daily. Oxygen therapy was necessary at this time as well. On January 5, he was given 12 grains at 10 30 a.m. and 12 grains at 1 30 p.m. The electrocardiogram revealed continuation of the arrhythmia (C). By this time the QRS complexes were definitely wider and measured approximately 0.18 second as compared to 0.11 second on the original tracing. No signs of quinidine toxicity were noted clinically. At 4 30 p.m. on the fifth, the ventricular rate was 100 per minute, with definite coupling. The electrocardiogram (D) revealed reestablishment of the sinus mechanism with regularly recurring ventricular premature contractions following every conducted ventricular beat. By this time the patient received a total of 114 grains of quinidine over a period of less than two and a half days. By January 7 the extrasystoles had disappeared and further changes in the evolution of the infarction may be seen on tracing E.

Quinidine intake was gradually reduced but continued in smaller doses for a 10 day period. Recovery was uneventful.

*Summary.* Myocardial infarction in a known hypertensive and coronary arteriosclerotic cardiac was complicated by a ventricular tachycardia in the second week of illness. This arrhythmia persisted for a period of approximately 55 hours and terminated after the patient had received 114 grains of quinidine in this period of time. No toxicity attributable to the drug was noted. Following the cessation of the arrhythmia, coupling due to ventricular premature contractions persisted for about 24 hours, and then disappeared. The QRS interval increased to 0.24 second under quinidine therapy.

*Case 4.* A 49 year old white cotton broker was admitted August 19, 1942, because of a series of attacks of retrosternal oppressive pain for two weeks prior to admission. The most severe and persistent attack occurred four days before admission and lasted for two days. This was accompanied by dyspnea at rest and a fall in blood pressure. He was a known hypertensive, and work-up in 1939 revealed a normal-sized heart, a blood pressure of 170 mm Hg systolic and 110 mm diastolic, and an electrocardiogram which showed moderately severe left axis deviation.

At the time of admission his blood pressure was 120 mm Hg systolic and 70 mm diastolic. The rhythm was irregular and the sounds were of poor quality. The rate varied from 80 to 120 per minute. It was difficult to evaluate the type of arrhythmia. A tentative diagnosis of coronary occlusion with ventricular extrasystoles and possible A-V block was made. This was confirmed by the electrocardiogram (8-19-42) which showed a very unusual series of tracings. The arrhythmia consisted of a 2:1 A-V block, followed by a persistent paroxysm of ventricular tachycardia with a rate

of approximately 125 per minute. There was one complex, luckily caught in Lead II, which suggested the diagnosis of posterior infarction. No friction rub developed. The sedimentation rate was 100 mm per hour. The patient was critically ill.

He was placed on quinidine sulphate, grains six, three times daily, and this dosage was continued for 11 days. On August 20 the electrocardiogram (A) showed a sinus

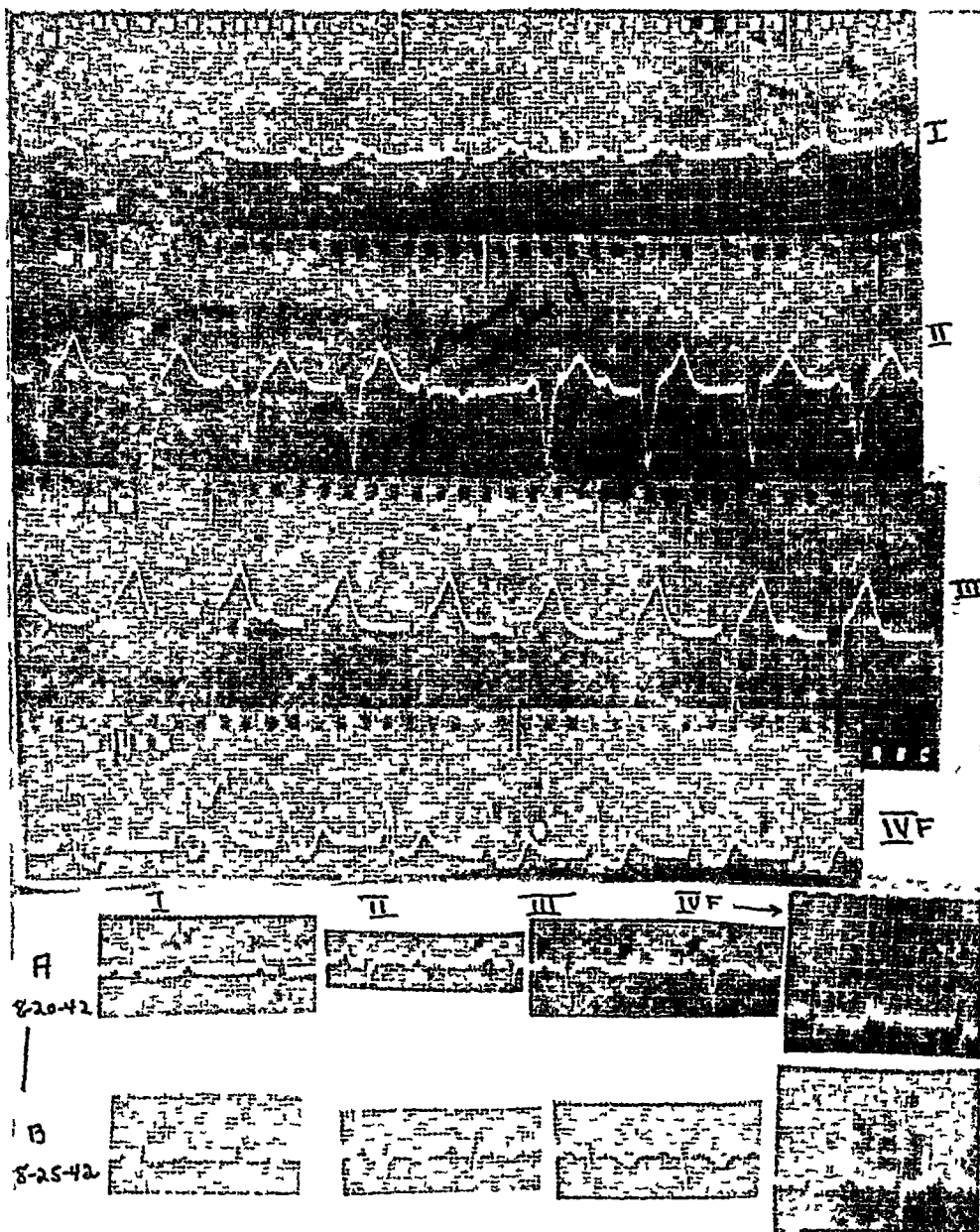
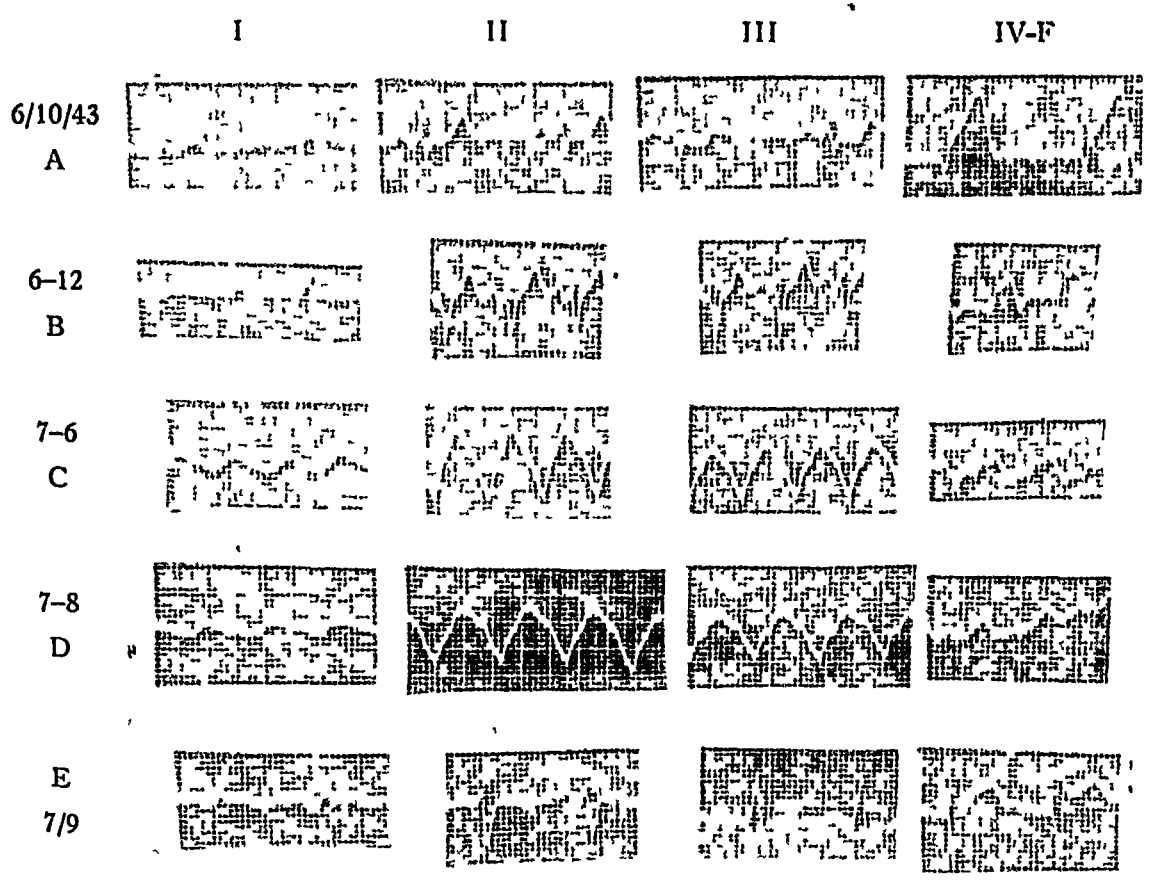


FIG 4 Case 4 A very unusual and interesting series of tracings. Lead I shows a 2:1 A-V block. Lead II shows runs of ventricular beats of bizarre configuration. There is one complex that suggested a diagnosis of infarction in this lead. This was proved by the subsequent tracings and the clinical course of the patient. Leads III and IV in the tracing dated 8-19-42 show the continuation of the abnormal rhythm. The rate was unusually slow. It is felt, however, that the tracing indicates a ventricular tachycardia because of the ectopic origin of the impulse in the "shower" of the ventricular systoles. Note the striking changes when the normal sinus rhythm supervenes in the subsequent tracings.

hythm with a 2:1 block and confirmation of the posterior wall infarction. Notwithstanding the 2:1 block, quinidine therapy was continued and on August 25 electrocardiogram (B) revealed a normal sinus mechanism with a 1:1 rhythm. His recovery from then on was uneventful.

**Summary** A 49 year old known hypertensive male was admitted with a posterior wall infarction of at least a few days' duration, complicated by a ventricular tachycardia and also a 2:1 A-V block. Quinidine in doses of 18 grams daily terminated



**FIG 5 Case 5** See text for details. This is a case of anterior wall infarction complicated by a ventricular tachycardia. Note the marked widening of the QRS complexes under quinidine therapy, as well as the reduction in the rate of the ectopic rhythm.

the ventricular tachycardia and did not prevent the return of the normal sinus mechanism. The academic question of whether or not this series of rapidly recurring bizarre QRS complexes represents multiple ventricular escape beats, or a true ventricular tachycardia, cannot be answered. I do not believe that they should be considered as separate and distinct entities. Whether or not spontaneous subsidence of the ventricular tachycardia would have taken place without quinidine is anybody's guess. No ventricular extrasystoles recurred following the cessation of the arrhythmia, while under quinidine therapy.

**Case 5** A 46 year old white lawyer was admitted June 10, 1942, with a history of severe squeezing retrosternal pain accompanied by shortness of breath. The pain radiated down both arms and had been present for one and a half hours at the time of admission. The past history was not relevant. Examination revealed a moderately thin white male, perspiring profusely and in obvious pain. There was slight cyanosis of the nail beds. The heart was not enlarged. There was regular sinus rhythm. The first sound over the apex was barely audible. There was no friction rub, no thrills or

murmurs Blood pressure was 110 mm Hg systolic and 74 mm diastolic A clinical diagnosis of myocardial infarction was supported by the electrocardiogram, which showed an acute anterior wall occlusion with low voltage (A)

The patient was given intravenous aminophyllin and morphine His pulse rose steadily and reached 140 per minute on June 12, and then slowly fell to a rate of 90 to 100 There were no ventricular extrasystoles present Electrocardiogram (B) showed further changes in the evolution of the anterior wall infarction and a more rapid sinus rate Oxygen was administered with favorable results, the patient becoming more comfortable and less dyspneic On June 26, he incurred an upper respiratory infection accompanied by a slight temperature rise This subsided rapidly On June 29 he again complained of pain in both shoulders, his temperature rose slightly and remained at a level of 100 to 101° F until July 13, 1944

On July 5, 1944, at 10 00 a m., he was found in shock The pulse rate was 166 per minute and barely perceptible The blood pressure was unobtainable There was no pain The rapid rate did not respond to carotid sinus pressure or ocular pressure He was sedated and started on quinidine therapy in gradually increasing doses, receiving 30 grains by July 6 Electrocardiogram (C) revealed a ventricular tachycardia with a rate of 160 per minute The QRS duration was 18 second The arrhythmia continued and quinidine was increased to 12 grains four times daily By June 8 his ventricular rate had slowed to 140 per minute and the QRS interval increased to 20 second (D)

The heart became larger clinically, and basal râles soon became apparent No digitalis, however, was administered He appeared relatively comfortable, and remained slightly febrile Quinidine was continued in doses of 12 grains every six hours, and on June 9 his rate dropped to 80 per minute and he experienced an abrupt change for the better in his condition The electrocardiogram (E) revealed a regular sinus rhythm with other relevant ST and T-wave changes Quinidine was gradually reduced during the remainder of his hospital stay, but the appearance of frequent extrasystoles necessitated increase in dosage, so that a dose of nine grains four times daily was required to suppress the ventricular premature contractions His recovery from then on was uneventful

*Summary* A 46 year old white male entered the hospital with an acute anterior wall occlusion which was complicated by a ventricular tachycardia in the fourth week of his illness He appeared in a terminal state on many occasions Quinidine in moderately large doses was administered The arrhythmia persisted for four and a half days One hundred and twenty grains of quinidine were given before the arrhythmia ceased, the highest daily dosage was 48 grains It was necessary to continue the administration of quinidine during the remainder of his hospital stay because of the appearance of ventricular premature contractions Nine grains four times daily appeared to be the optimal dosage

In retrospect, it is believed that quinidine was not given in sufficiently large doses and the intervals of administration were too long, but this is a difficult point to prove

*Case 6* A 51 year old white male, a known hypertensive of moderate severity, was admitted May 23, 1943, with a history of severe retrosternal oppression, radiating to both shoulders This began May 18, 1943, and recurred three times in four days The last attack occurred on the day prior to admission and persisted, although of lesser severity, up to the time of admission On admission he appeared critically ill and was in mild shock The blood pressure was 86 mm Hg systolic and 60 mm diastolic The heart was not enlarged The sounds were extremely poor in quality There was no gallop or pericardial friction rub There was no evidence of congestive failure The peripheral and retinal vessels were sclerotic A diagnosis of recent myocardial infarction was confirmed by electrocardiography (A) The rhythm was regular sinus and the infarction was on the anterior wall



Intravenous aminophyllin, together with sedation and oxygen, were administered. Singultus was extremely troublesome and did not respond to the usual modes of therapy. He merged slowly into left-sided failure and it was believed advisable to digitalize the patient cautiously. On May 29, one and one half grains of digitalis were given twice daily, and this was continued, with little change in his condition. His hiccups stopped on June 1, at which time his temperature and pulse rate returned to normal. There were no extrasystoles. The sounds continued to remain extremely poor. The blood pressure was 96 mm Hg systolic and 62 mm diastolic. On June 2, at 2 20 p m, his ventricular rate rose suddenly to 200 per minute. A diagnosis of ventricular tachycardia was confirmed by electrocardiography. After a test dose of three grains of quinidine he was given 15 grains, followed by six grains every two hours. The patient died at 2 40 a m June 3, 1944. There was equivocal evidence of embolic occlusion of the right femoral artery, just prior to death. He received 48 grains of quinidine in a little less than 12 hours.

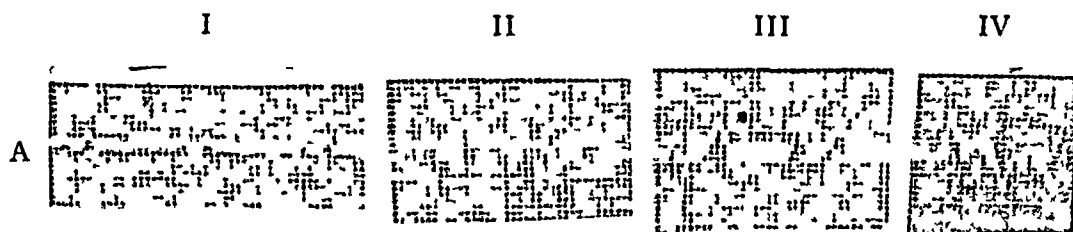


FIG 6 Case 6 The anterior wall infarction is seen. The electrocardiogram showing the ventricular tachycardia is not available.

*Comment* Ventricular tachycardia complicating an anterior wall infarction ended fatally approximately 12 hours after its onset. During this time 48 grains of quinidine had been administered. This patient received very small doses of digitalis for a period of four days prior to death, eight cat units having been administered in four days. It appears unlikely that digitalis in the doses given played any etiological part in this arrhythmia.

Unfortunately, the electrocardiogram showing the ventricular tachycardia in this case is not available.

*Case 7* A 59 year old negro male was admitted May 24, 1943, acutely ill, mentally confused, and in severe congestive failure. The pulse was not perceptible and no blood pressure reading could be obtained. There was definite clinical evidence of forward failure (shock) as well as generalized anasarca, ascites, dyspnea and orthopnea. The only history obtained from his family was the fact that patient's blood pressure had been high for an unknown period. The heart rate was rapid and regular, approximately 200 per minute. The heart sounds were poor. The heart was enlarged.

He was placed on digitalis and sedated prior to cardiac consultation. He was seen in consultation on May 25 and a diagnosis of ventricular tachycardia was confirmed by electrocardiograph (A). He was placed on 9 grains of quinidine orally every three hours, day and night, and by May 29 he had received a total of 315 grains. By this time the ventricular rate had slowed to 118-120 per minute, and the patient felt somewhat better, although he remained in severe congestive failure. Electrocardiogram (B) revealed persistence of the ectopic rhythm with a rate of 118 per minute, the QRS interval had widened to almost 0.18 second. On May 30 his quinidine intake had been discontinued by the ward surgeon so that he received only 18 grains for the entire 24-hour period. Electrocardiogram of May 31 again revealed a rapid rate (205 per minute) with a decrease in QRS conduction time (C). Quinidine was then increased to 12 grains every three hours on May 31, augmented with

potassium citrate in small doses. This dosage was continued through June 1, so that he received 132 grains on May 31 and June 1, and 60 grains more on June 2. At 3 00 p m on June 2 his ventricular rate was 60 per minute. Electrocardiogram (D) revealed a sinus mechanism with a complete A-V dissociation. The total amount of quinidine administered in nine days was 525 grains. Signs of toxicity by this time included a moderately severe diarrhea, vomiting, and abdominal pain. From then on quinidine was administered in 6 grain doses, four times daily, until June 15 and then reduced to three grains, three times daily. Other measures to combat the severe congestive failure including mercurial diuretics, ammonium chloride, and sedation

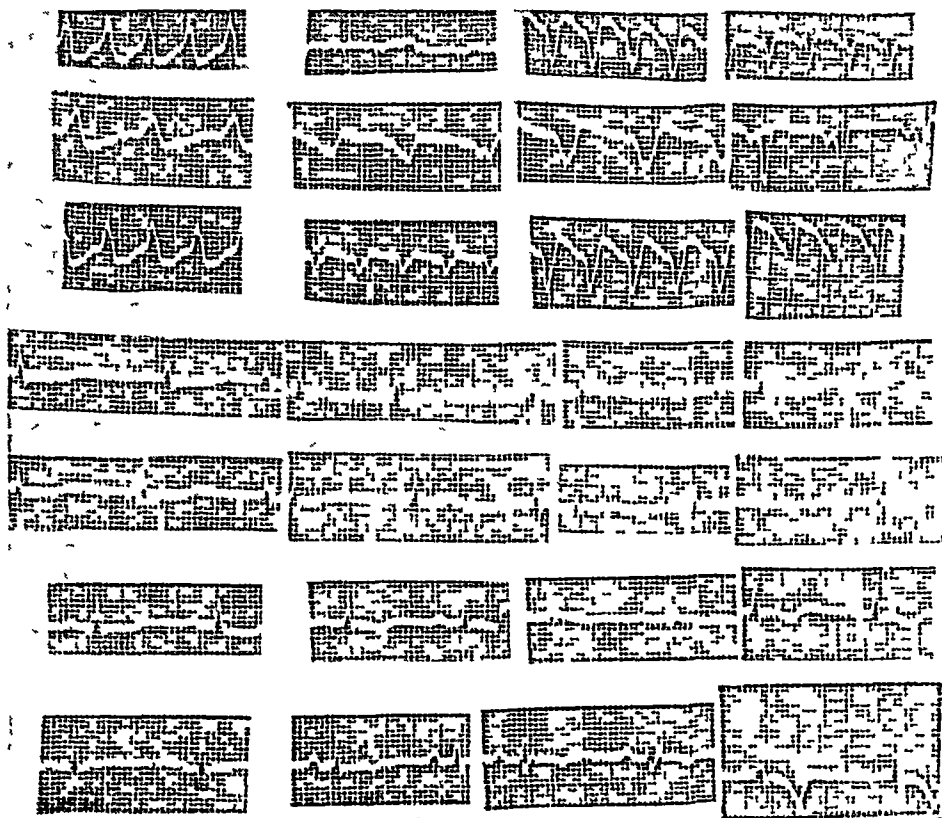


FIG 7 Case 7. See text for details. Note the transition stage of complete A-V block in tracings D and E. In tracing B note the marked slowing, followed by the return to a more rapid rate as seen in tracing C. The latter record was taken shortly after the quinidine was temporarily reduced. The reestablishment of the normal sinus mechanism is seen in the last record.

eventually enabled this patient to become ambulant. He was discharged with maximum benefit with a moderately severe diminution in his cardiac reserve. A probable nodal rhythm is seen on tracing E, and regular sinus mechanisms are seen on tracings F and G. Note the deep T-wave inversion in Lead IV-F. During his hospital stay he had received a total of 922 grains of quinidine, 525 of which were given prior to the termination of the ectopic rhythm.

*Comment.* A 59 year old negro with hypertensive and coronary arteriosclerotic cardiac disease was admitted in severe congestive heart failure with a ventricular tachycardia of unknown, but probably extended duration. Prior to consultation he was placed on digitalis, but later treated with massive doses of quinidine sulphate. In a period of nine days 525 grains were administered orally after which the tachy-

cardia gave way to a slow rate with complete A-V dissociation and then to a normal sinus mechanism. Signs of toxicity included vomiting, foul diarrhea, and abdominal pain, although the patient had vomited persistently prior to the introduction of quinidine. The patient was finally discharged able to get about, albeit with a diminished myocardial reserve.

Case 8 was again admitted June 16, 1944, in severe failure, with a history of rapid heart action for two weeks prior to admission. He stated that he had done quite well since his discharge, and it could not be ascertained whether or not he had been taking digitalis. With our experience with negroes in this section of the country it seemed highly improbable that he had been taking the drug. The rate was 200 per minute, the sounds poor, the blood pressure unobtainable. Again, forward failure was engrafted upon severe congestive failure. There was no response to ocular or carotid sinus pressure. Vomiting was persistent. The patient was uremic and relatively anuric.

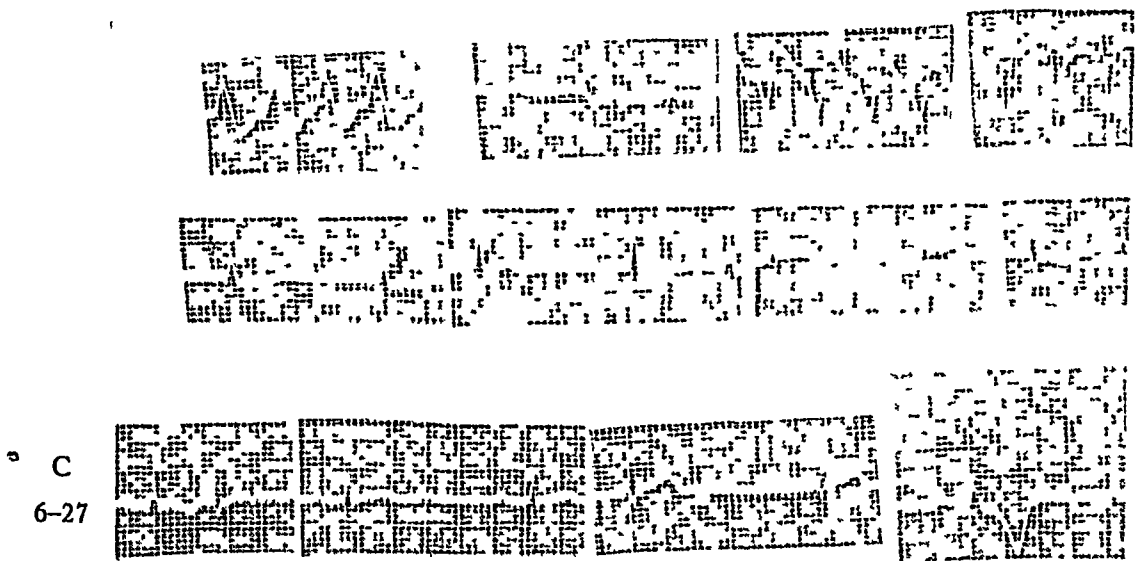


FIG 8 Case 8 See text for details. Again the same sequence from ventricular tachycardia to complete A-V block to normal sinus rhythm is seen.

Quinidine therapy was instituted on the day of admission, in doses of three grains every two hours, day and night, the dose was doubled on the seventeenth. On the seventeenth, electrocardiogram revealed that the arrhythmia had broken, again complete A-V dissociation with a slow idioventricular rhythm was exhibited (B). Digitalis, in conjunction with quinidine, was administered, in addition to hypertonic glucose, intravenously, and mercurial diuretics. With this therapy his urinary output improved rapidly and signs of congestive failure diminished. The urinary output exceeded 6000 cc daily and the non-protein nitrogen fell rapidly. Final tracing (C) dated June 27, 1944, revealed a normal sinus mechanism. The patient was discharged feeling well, and ambulant, with minimal edema. Seventy-two grains of quinidine over a two day period were required to terminate the arrhythmia.

*Comment* A second paroxysm of ventricular tachycardia in a 60 year old negro male, with hypertensive and arteriosclerotic heart disease, responded favorably to large doses of quinidine given frequently by the oral route. The duration of the attack was probably 14 to 16 days. There was no clinical or laboratory evidence of myocardial infarction. Deep T-wave inversion in Lead IV-F similar to that seen on the prior admission occurred. Again, the interesting sequence of events included the

intermediate stage of complete A-V dissociation. This was not considered a contraindication to either digitalis or quinidine administration. The amount of quinidine required to terminate the arrhythmia was decidedly less than that needed in the prior attack, although the short interval of administration was probably an important factor in the favorable outcome.

**Case 9** A 46 year old white male had known coronary artery disease. He was known to have had attacks of paroxysmal rapid heart action in the past which, on at least one occasion, was proved to be ventricular in origin. He was not a known hypertensive. He was admitted September 14, 1942, with a history of an abrupt onset of rapid heart action 48 hours prior to admission. Attempts at terminating the ectopic rhythm by his local physician included the use of quinine and digitalis, but to no avail.

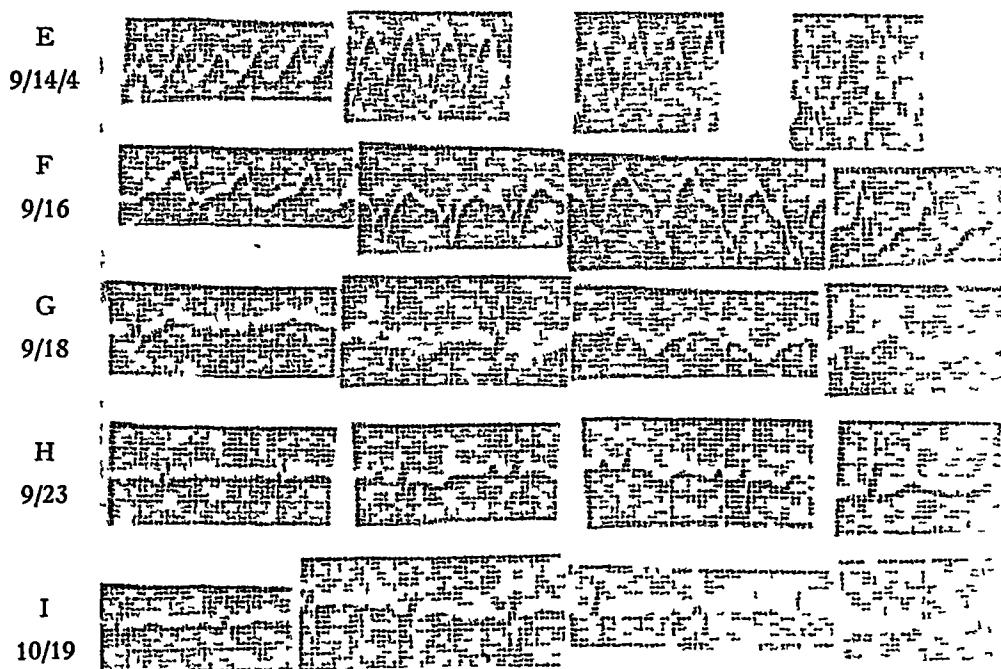


FIG 9 Case 9 Ventricular tachycardia rate slightly above 200 per minute. Note the widening of the QRS complexes following quinidine therapy with a slowing of the ectopic ventricular rate. When sinus rhythm was reestablished the T-waves became inverted in Leads II and III. This persisted for approximately one month and occurred in the absence of Q-waves and reciprocal ST changes (from the author's case published in the *Journal of Laboratory and Clinical Medicine*, June 1944).

At the time of admission examination revealed a regular ventricular rate of 216 per minute. The pulses were barely perceptible, the blood pressure could not be obtained, the sounds were of fair quality. No murmurs were audible. The heart was not enlarged. He was in shock. The rate could not be altered by carotid sinus or orbital pressure. There was moderate peripheral and retinal sclerosis. The patient was placed on quinidine sulphate, grains six, four times daily. On September 15, 1942, there was no change in rate or rhythm, six grains of quinidine every two hours were administered, and the patient was sedated with morphine. By 4:45 p.m. on September 15, 1942, he had had 48 grains of quinidine. This dosage was continued through midnight September 15, 1942, and again at 7:30 a.m. September 16, 1942. By the sixteenth his rate was reduced to 112 per minute and was regular. Electrocardiogram (see figure) revealed persistence of the ectopic rhythm, with a rate of 132

per minute. The QRS interval increased considerably and measured 0.19 second as compared to 0.16 second on the original tracing. On the morning of the eighteenth his ectopic rhythm had given way to a regular sinus one, with a rate of 84 per minute. By this time he had received 174 grains of quinidine in three days. Six-grain doses every four hours were continued day and night for two days and then the dosage was gradually reduced. His recovery was uneventful.

*Comment.* A case of ventricular tachycardia of six days' duration was terminated abruptly with the aid of fairly large doses of quinidine sulphate given orally. Six grains every two hours was the largest dose administered to this patient. No toxic effects were observed clinically. The electrocardiogram revealed widening of the QRS complexes with a slowing of the rate, and then return to normal sinus rhythm. Most interesting was the inversion of the T-waves seen in Leads II and III. These inversions, unaccompanied by Q-waves or reciprocal S-T changes, persisted about one month and then returned to their original upright configuration. Whether they indicate "myocardial fatigue" or manifest coronary insufficiency brought on by the tachycardia is not known. Nevertheless, it would appear that they are not necessarily of ominous prognostic importance. This case was reported in detail elsewhere.<sup>12</sup>

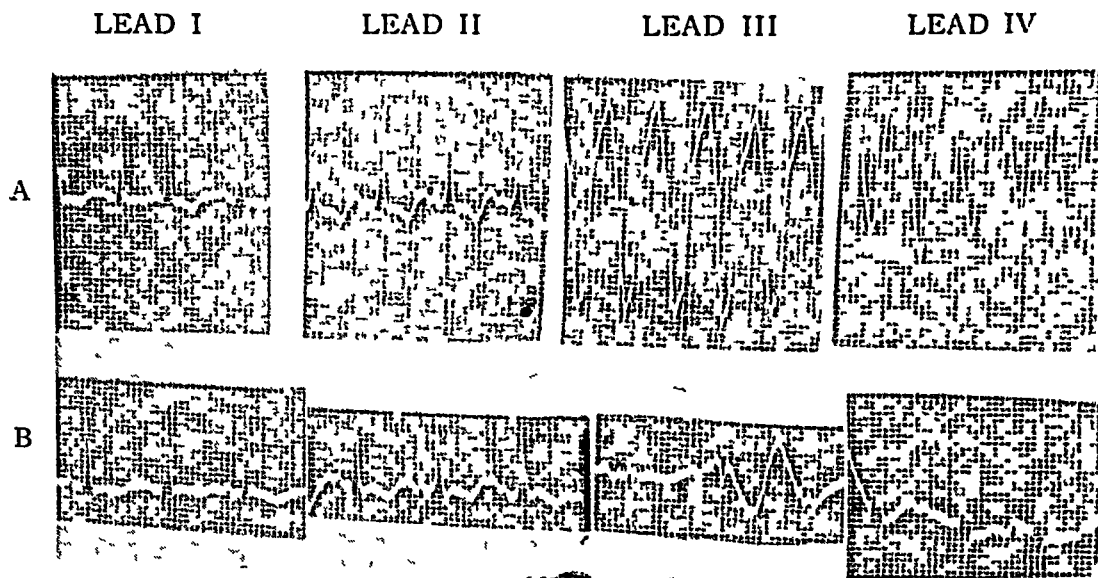


FIG 10 Case 10 See text

*Case 10.* A 54 year old negro male had been hospitalized for a period of two years because of severe diabetes and multiple sclerosis. He was known to have had hypertensive and coronary arteriosclerotic cardiac disease, his blood pressure having been moderately elevated. On October 22, 1944 his diabetes became exceedingly difficult to control, the patient became drowsy and his urine showed a marked glycosuria. His insulin was increased and other treatment was directed toward his impending coma.

On October 26 his ventricular rate suddenly rose to 180 per minute, the patient went into shock, and appeared in a terminal state. Cheyne-Stokes respirations were present. Electrocardiogram (A) revealed an interesting combination of arrhythmias, Lead I showing an auricular fibrillation, Lead II a regular sinus rhythm with a PR interval of 0.09 second and Leads III and IV revealed a ventricular tachycardia with a rate of 182 per minute.

With this tracing confirming the clinical impression of ventricular tachycardia, the patient was given 15 grains of quinidine orally and then 9 grains every three

hours day and night. This dose was continued throughout the night, during which time the arrhythmia ceased. The dosage was subsequently reduced to 3 grains every four hours. Electrocardiogram (B) taken on October 27 revealed a return to a regular sinus mechanism with a few ventricular premature contractions. These subsequently disappeared.

*Summary* A 54 year old negro male with diabetes and known hypertensive and coronary disease developed a ventricular tachycardia during a period of uncontrolled hyperglycemia and possible acidosis. Quinidine in large doses succeeded in terminating the arrhythmia within a period of seven hours, after a total of 24 grains of the drug in the same period of time.

## DISCUSSION

The ominous prognostic significance of paroxysmal ventricular tachycardia is universally known. It is felt, however, that the underlying heart disease is the ultimate determiner with respect to the immediate outcome. This is particularly true in cases of recent coronary thrombosis. It is difficult, therefore, to arrive at any reliable mortality statistics with respect to this rhythm. That it is high is well known, and the gravity of this complication following cardiac infarction need not be further discussed. The recovery of seven of the eight treated cases which comprise the body of this report is sufficiently striking to warrant reporting.

In this series the ages ranged from 46 to 60. This is in line with the average age of the veteran of World War I at this time, and does not lend itself to any type of analysis. The arrhythmia complicated infarction in five of the 10 cases. In four of these the infarct was situated on the anterior wall, and in one it was situated on the posterior wall. In one of the 10 cases no underlying heart disease could be demonstrated, whereas coronary disease, alone or associated with hypertension was present in the remainder. Hypertension was present in six, and the anginal syndrome was present in two of the 10 cases. None of the cases gave any history of rheumatic fever and there was no evidence of valvular disease in any of the patients.

The rôle played by digitalis in the causation of this arrhythmia has been stressed by many authors. In Williams and Ellis'<sup>8</sup> series of 36 cases abstracted from the records of the Boston City Hospital, digitalis had been administered in 17. In eight of these there was no apparent question as to the association of the arrhythmia and digitalis. In the other remaining nine cases the amount of digitalis administered was in excess of the theoretic requirement, and no other cause for the attack was apparent. With reference to the cases reported here only one of the 10 had digitalis prior to the onset of the ventricular tachycardia. This patient (case 6) had been given only eight cat units in a period of four days. It would appear highly unlikely that this drug had any causal relationship to the establishment of this ectopic rhythm.

The ventricular rate at the time of the establishment of the arrhythmia varied from 125 to 216 per minute. Definite and unequivocal slowing of the ventricular rate followed the administration of the drug in all cases. As

stated above, widening of the QRS interval was a definite accompaniment of quinidine exhibition, in many cases the prolongation assuming considerable magnitude. There did not appear to be any relationship between the initial rate, the width of the QRS interval, the duration of the attack and the final outcome.

Of the untreated cases, one case (case 2) reverted to a normal sinus mechanism following sedation with morphine. The other one (case 1) died within a few hours after admission, following a massive infarction of the anterior wall of the left ventricle. The remaining eight cases were alive for a sufficient length of time to permit adequate therapy. Of these eight there was only one death (case 6), and this patient died within 12 hours after the exhibition of this arrhythmia, having received 48 grains of quinidine in this period of time. He had clinical evidence of massive infarction of the anterior wall of the left ventricle together with a borderline low voltage electrocardiogram. Whether or not this patient would have died even without the complicating ventricular tachycardia is conjectural. He appeared in extremis prior to the exhibition of this arrhythmia. The remaining three treated infarction cases which recovered appeared just as ill, however.

There did not appear to be any relationship between the amount of quinidine given and the ultimate outcome. The most persistent case required 525 grains over a period of nine days. The least amount given was 24 grains in 24 hours. This was a case of posterior wall infarction, and the arrhythmia was definitely paroxysmal (case 4). The QRS intervals varied, at the onset, between 0.11 and 0.18 second. In the case which was treated and died, the electrocardiogram showing the ectopic rhythm is not available for analysis. The total duration of the arrhythmia, including the time it was present prior to admission, varied between seven hours and 16 days. The longest duration while under treatment was nine days.

The only evidence of quinidine toxicity, in spite of the relatively large doses administered, was persistent diarrhea and vomiting in one case. In view of the critical condition of this patient and because it was felt that the continuation of the tachycardia would eventually kill the patient, the drug was pushed to the limits of the patient. The outcome was successful. Following the cessation of the arrhythmia two of the patients exhibited T-wave inversion in more than one lead. There was no clinical or electrocardiographic evidence of myocardial infarction. That the T-wave inversion was not the result of quinidine therapy has been discussed elsewhere<sup>12</sup>. These changes are depicted in the tracings accompanying cases 2 and 9. In case 3 coupling due to ventricular premature contractions preceded the reestablishment of the normal sinus mechanism. In case 4 a 2:1 A-V block preceded the sinus mechanism and this conduction defect was not adversely affected by further quinidine administration. The paroxysms in cases 7 and 8 passed through a state of complete A-V dissociation prior to the appearance of a normal sinus rhythm. Quinidine did not prevent the evolution of this sequence.

## SUMMARY

1 Ten cases of ventricular tachycardia are reported and discussed from the standpoints of underlying heart disease, causal effects of digitalis, ventricular rates, QRS intervals and the presence of congestive cardiac failure. Digitalis was not causal in the production of the arrhythmia in any of the reported cases. Five of the 10 cases complicated myocardial infarction. In one case no underlying cardiac disease could be demonstrated. In the remaining cases coronary disease, alone, or in association with hypertension was easily established.

2 Eight of the 10 cases were treated with relatively large doses of quinidine. Seven of these cases recovered. Three of these paroxysms complicated myocardial infarctions, and were successfully treated. The only death occurred in a patient who had a massive anterior wall infarction and who appeared in a terminal state even prior to the onset of the arrhythmia.

3 The total amount of quinidine required to terminate the arrhythmia varied greatly from case to case. Large doses were given unhesitatingly with extremely gratifying results. Toxic signs and symptoms were negligible. The QRS interval was disregarded as an index of quinidine toxicity.

4 The recent literature bearing on the subject has been discussed. Relatively few reports dealing with the effect of large doses of quinidine on this arrhythmia have been noticed.

5 From a review of this series, and as a result of the perusal of the sparse recent literature, quinidine in adequate, and massive doses if necessary, is recommended in the treatment of ventricular tachycardia. There does not appear to be any unequivocal evidence that its administration following acute coronary occlusions is in any way detrimental.

## BIBLIOGRAPHY

- 1 McMILLAN, R. L. Ventricular tachycardia as a therapeutic problem in coronary thrombosis, *South Med Jr*, 1943, xxxvi, 800.
- 2 REICH, NATHANIEL E. Successful use of a massive dose of quinidine in a case of intractable ventricular tachycardia, *Am Heart Jr*, 1944, xxviii, 256.
- 3 LEVINE, S. A. Quoted by REICH.<sup>2</sup>
- 4 GOLD, HARRY. Quoted by REICH.<sup>2</sup>
- 5 LEVINE, S. A., and FULTON, M. H. Effect of quinidine sulphate on ventricular tachycardia. Clinical observation, *Jr Am Med Assoc*, 1929, xlii, 1162.
- 6 VIKO, L. E., MARVIN, H. M., and WHITE, P. D. A clinical report on the use of quinidine sulphate, *Arch Int Med*, 1923, xxxi, 345.
- 7 FISHBERG, ARTHUR M. Heart failure (2nd edition), 1940, Lea and Febiger, Philadelphia.
- 8 WILLIAMS, CONGER, and ELLIS, LAURENCE B. Ventricular tachycardia: an analysis of thirty-six cases, *Arch Int Med*, 1943, lxxi, 137.
- 9 WOODRUFF, LEWIS W. Present day uses of quinidine, *Illinois Med Jr*, 1934, lxx, 144.
- 10 STEMPIEN, STEPHEN J., and KATZ, KERMIT H. Quinidine and potassium in the treatment of refractory paroxysmal ventricular tachycardia, *Am Heart Jr*, 1942, xxv, 555.
- 11 CONEAU, WILFRED J. Cardiac drugs—their rational use, *Jr Maine Med Assoc*, 1941, xxxii, 10.
- 12 ZIMMERMAN, S. L. Transient T-wave inversion following paroxysmal tachycardia, *Jr Lab and Clin Med*, 1944, xxix, 598.



# CASE REPORTS

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## ANEURYSM OF AORTA WITH COMPRESSION OF PULMONARY ARTERY AND LEFT AURICLE \*

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### CASE REPORT

THE patient, a 42 year old Spaniard, was admitted on September 15, 1943, with the chief complaint of dyspnea of six months' duration

About six months previously the patient caught cold with which he had a stuffy nose, sore throat and cough. He was treated symptomatically by his private physician without improvement and about four months prior to this admission was hospitalized elsewhere for pneumonia. He remained there about one week and then tried to return to work as a grocery clerk, but had to stop because of dyspnea on the slightest exertion, and weakness. Following this, despite rest, he became progressively worse until two days before admission, he was obliged to seek hospitalization. Orthopnea and nocturnal dyspnea had been present for one week. There had never been any edema. He had lost weight steadily, a total of 35 pounds, and his chronic cough of several years' duration had become worse. Sputum was scant, mucoid, never blood streaked. In addition, morning vomiting was often present during the preceding four months, but had become less frequent during the last two months. There also had been some abdominal pain of crampy nature, usually after eating, and relieved by vomiting. The vomitus was greenish and sometimes contained flecks of blood at the end of the vomiting spell. The bowels had been regular, the stools were never tarry and contained no frank blood.

There was a history of having worked for nine years in soft-coal mines. The patient believed his cough started some time during this period, but he had never been dyspneic until six months before admission.

The family history was not significant, except that the patient's father had died of heart disease.

There was a history of syphilis, contracted at the age of 14, which was treated when a secondary rash appeared. He had received intravenous and intramuscular medication over a two months' period. The patient denied ever having had gonorrhea. At the time of his hospitalization for pneumonia, the Kahn reaction had been positive.

*Physical Examination on Admission* Temperature 98.6° F Pulse 100 Respirations 28 Blood pressure 130 mm Hg systolic and 70 mm diastolic

*General Appearance* The patient appeared chronically and acutely ill, sitting up in bed, coughing and wheezing. There was mild dyspnea but no orthopnea. Cyanosis of the nail beds was present, but not of the lips.

*Head* Extraocular movements were normal. Pupils showed normal reactions. The conjunctivae and fundi were normal. The nose was negative. The tongue was in the mid-line and coated. The pharynx was red and the teeth foul.

\* Received for publication October 6, 1944

From the First Medical Division, Bellevue Hospital, New York City, Dr. I. Ogden Woodruff, Director

**Neck** The veins were distended, did not pulsate, and filled from above. The trachea was in the mid-line and the thyroid not enlarged.

**Heart** The point of maximum impulse was in the fifth space at the mid-clavicular line. The apical sounds were of rather poor quality.  $P_2$  was greater than  $A_2$ . The rhythm was regular with a rate of 100. Over the apex, there was a long, blowing systolic murmur and a short presystolic blow, heard with the patient in the left lateral recumbent position. No thrill was palpable.



FIG 1 Left ventricle and aneurysm

**Lungs** There was diminished tactile fremitus over the left lower lobe. Many rhonchi, squeaks and wheezes were present, especially when the patient had paroxysms of coughing which was wheezing in character.

**Abdomen** The liver was tender and enlarged, three fingers below the costal margin. The spleen was not palpated and no masses were present.

**Extremities.** Cyanosis of the nail beds was present. Clubbing and edema were absent.

**Reflexes** Were normal.

**Rectal** There were no tenderness, masses or enlargement of the prostate.

**Course.** The temperature ranged between  $98^{\circ}$  and  $101^{\circ}$  F, the pulse between 80 and 128, the respirations between 18 and 24. The patient became markedly dyspneic,

orthopneic and cyanotic, despite treatment with morphine, aminophylline, mercupurin, digitalis and low salt diet. The neck veins became more distended, and the liver enlarged further and some observers thought that expansile pulsation was present. No evidence of moisture in the lungs was ever noted. The cardiac signs varied somewhat with different observers. All, after the third day, heard a diastolic murmur at the base and along the left sternal border, most heard a diastolic murmur at the apex also, as well as a systolic murmur. The majority thought that the second pul-



FIG 2 Right ventricle and pulmonary artery with the area of indentation and erosion caused by aneurysm

monic sound was accentuated and louder than the second aortic sound. The pulse was not Corrigan in type. The course was rapidly downward and he died on September 23, eight days after admission. No râles were heard in the lungs until pulmonary edema appeared in the final few hours.

An electrocardiogram revealed a sinus rhythm with a tachycardia and a delayed A-V conduction time (prolonged P-R interval).

A roentgenogram of the chest was interpreted by the roentgenological department as follows: "Heart enlarged in all diameters, widening of the supracardiac aorta. Configuration was that of mitral disease."

Fluoroscopic examination by one of the attending staff revealed enlargement of the left auricle and left ventricle, and apparent enlargement of the conus

The venous pressure was 260 mm water. Circulation time with decholin, 90 seconds, with ether 60 seconds

Urinalyses were normal, except for two-plus albumin. The Wassermann reaction was anticomplementary and the Kahn four plus. The blood count was normal except for a mild hypochromic anemia. The erythrocyte sedimentation rate was 9 mm per hour



FIG 3 Left auricle.

*Clinical Diagnosis* Syphilitic heart disease with aortic insufficiency and aneurysm of ascending aorta, rheumatic heart disease with aortic insufficiency and mitral stenosis and insufficiency

*Autopsy Report* (Drs Harvey and Spain) The body was that of a moderately well developed, well nourished, white male, 42 years of age. The scalp hair was grayish-black, fine and plentiful. The axillary, chest and pubic hair were of normal masculine distribution. The skin was normal in texture and turgor. There was marked cyanosis of the face, neck and nailbeds. The pupils were regular in outline and equal. The conjunctivae were slightly injected but otherwise showed no changes.

There were no changes referable to the ears, external nares, or mouth. The trachea was in the mid-line. The thyroid was not palpable. No lymph nodes were felt in the axillary, cervical or inguinal regions. The chest was symmetrical. The abdomen was scaphoid in contour. The genitalia were normal in size, shape and appearance. There was no edema or clubbing of the upper and lower extremities. There was a gaping wound in the left antecubital fossa which measured 2 cm in length (phlebotomy wound).

The usual Y-shaped incision was made. The subcutaneous fat was slightly reduced in amount. The red muscles were moderately well developed. When the abdomen was opened the peritoneum was seen to be smooth and glistening. There were 1,000 c c of clear yellow fluid in the peritoneal cavity. The liver extended 5 cm below the right costal margin. The left dome of the diaphragm was at the fifth interspace, the right dome was at the fourth rib.

Both pleural cavities were dry. The left pleural cavity was free of adhesions. There were many firm fibrous adhesions binding the right lung to the chest wall. It was necessary to remove this lung extrapleurally as the adhesions could not be broken.

**Heart.** On section of the right heart the endocardium was seen to be smooth and glistening. There was a moderately large thrombus occupying the right auricular appendage. The right auricle was free of thrombi and was not dilated. The foramen ovale was closed. The tricuspid valve cusps were thin and delicate and the chordae tendineae were neither shortened nor fused. There was neither fusion nor separation of the pulmonic valve cusps at the commissures and the cusps showed no changes. The right ventricular wall measured 7 mm. The columnae carnae were slightly flattened. The myocardium was uniformly light brown in color.

On section of the left heart the endocardium was seen to be smooth and glistening except for two plaques in the left auricle. The larger plaque measured 3 by 2 cm, the smaller measured 1 cm in its greatest diameter. These areas were covered by friable shaggy masses which were more or less firmly attached to the endocardium. The mitral valve cusps were thin and delicate as were the chordae tendineae. The latter were neither shortened nor fused. The left ventricular wall measured 1.4 cm. The myocardium was uniformly light tan in color. The aortic valve cusps were thin and delicate. There was a questionable separation of one commissure, however, there was light fusion of the other two cusps at their junction. Just above the valves there was a large saccular aneurysm of the aorta. This aneurysm bulged anteriorly and laterally. Its walls were thick, and the endothelial surface was covered by a shaggy friable light brown material. A large thrombus occupied the lumen of the aneurysm. The lumen of the aorta ran posteriorly to the aneurysm. The aneurysm was adherent to the posterior surface of the pulmonary artery and markedly diminished its lumen. At the point of greatest narrowing of the pulmonary artery (4 cm above the valve), there was a large irregular plaque of friable reddish-brown material which was firmly adherent to the intima. This plaque measured 3 by 0.5 cm. In a similar fashion, but to a less extent, the aneurysm was adherent to and bulged into the left auricle.

There was partial stenosis of the coronary ostia. This was more marked on the left than on the right. In the first portion of the ascending aorta, there were numerous fine longitudinal wrinklins of the intima. The arch and thoracic portions of the aorta showed numerous light yellowish-gray plaques on the intimal surface. There were, in addition, minimal arteriosclerotic plaques throughout the entire course of the aorta. The renal arteries showed no changes.

**Lungs.** The lungs together weighed 1,100 gm. The pleural surfaces of the lungs were smooth, grayish-black in color and glistening. On section the parenchyma of the left lung, which was cottony to touch and crepitant throughout, was seen to be uniformly grayish-black in color. The pleural surface of the right lung was shaggy in appearance and yellowish-black in color. The parenchyma was cottony to touch,

crepitant throughout and uniformly grayish-black in color. There was neither exudate nor fluid in the parenchyma or bronchioles of either lung.

The tracheobronchial lymph nodes were slightly enlarged, black and firm. On section a uniformly black surface was seen.

**Liver** The liver weighed 1,450 gm. The capsule was smooth, glistening and light gray in color except that portion of it which covered the lower pole of the right lobe. Here the capsule was thickened, opaque and yellowish-gray in color. On section the



FIG 4 Roentgenogram of chest

moderately firm parenchyma was seen to be yellowish-red in color. It had a 'nutmeg' appearance and the lobular architecture was accentuated. The portal vein, hepatic artery, hepatic, cystic and common bile ducts showed no changes.

**Gall-Bladder** The thin walled gall-bladder contained 80 c.c. of a thick dark green viscid bile. The dark green mucosa was velvety in appearance. No stones were present in the biliary tract.

**Pancreas** The firm yellowish-white pancreas was normal in size and shape. On section the lobular architecture was seen to be well preserved.

**Spleen** The spleen weighed 120 gm. The gray, glistening capsule was slightly wrinkled. On section the Malpighian corpuscles stood out clearly as did the trabeculae against the background of the deep reddish-purple firm pulp.

**Adrenals** The adrenals were normal in size, shape and consistency. On section the yellow cortex and grayish-brown medulla were seen to be normal in width and appearance.

**Kidneys** Each kidney weighed 200 gm. The capsule of the right kidney stripped with ease, revealing a smooth, reddish-brown cortex. On section the cortex was seen to be normal in width and was easily demarcated from the medullary pyramids which were of the same color. The open pelvis, calyces and ureter were not altered. The left kidney was like the right in all respects.

**Bladder** The bladder was distended by a moderate amount of turbid yellowish urine. The mucosa which was slightly trabeculated was yellowish-white in color. The ureteral and urethral orifices were patent.

**Prostate** The prostate was normal in size and shape and on section the parenchyma was seen to be firm, smooth and white. The testes were normal in size, shape and consistency. On section the light grayish-brown tubules strung out with ease.

**Gastrointestinal Tract** The esophageal wall contained many longitudinal wrinkleings. The mucosal surface was white in color. The stomach contained a small amount of dark gray mucoid material. Many rugae were present. The mucosa was dark red in color and a few petechial hemorrhages were seen. The small intestinal mucosa was also dark red in color but no other changes were seen. The ascending, transverse and descending colon were unaltered. There were a few scattered small diverticula of the sigmoid colon. These diverticula contained fecal material and were continuous with the lumen of the colon. The rectum was normal in appearance.

**Bone Marrow** The deep red vertebral bone marrow was normal in appearance.

**Organs of the Neck and Brain** Not examined.

**Microscopic Report** **Heart** **Right Ventricle** The muscle fibers were enlarged as were their bizarre nuclei. There was a moderate amount of perivascular fibrosis present. The epicardium showed no changes.

**Left Ventricle** The endocardial surface was covered by a thrombus which was undergoing early organization. The normal architecture of the irregularly thickened endocardium was disrupted by areas of hemorrhage, necrosis and accumulations of lymphocytes and polymorphonuclear leukocytes. Numerous dilated and congested capillaries and fibroblasts were seen in the deeper layers of the endocardium. Lymphocytes, polymorphonuclear leukocytes and connective tissue were present between the muscle fibers and around the blood vessels in the myocardium. Beneath the myocardium the wall of the aneurysm could be seen. The superficial surface of the aneurysm was covered by a thrombus. The wall itself was composed of dense acellular fibrous tissue. Dilated and congested blood vessels surrounded by lymphocytes and polymorphonuclear leukocytes could be seen in the depth of the aneurysm wall.

**Right Auricular Appendage** The endocardial surface of the appendage was covered by thrombus and by clot. The endocardium was slightly thickened by lymphocytic and polymorphonuclear leukocytic infiltration. Lymphocytes were also present around the blood vessels in the myocardium.

**Aortic Valve** The aortic cusps and the intervening commissure showed no changes other than fusion.

**Pulmonary Artery and Aneurysm** The intimal surface of the pulmonary artery was covered by thrombus. Necrotic polymorphonuclear leukocytes and lymphocytes were seen in the intima. The intima was further thickened by fibroblasts. All the adventitia and the greater portion of the media were replaced by a necrotic amorphous eosinophilic material in which the remnants of polymorphonuclear leukocytes could be seen.

**Thoracic Aorta** The intima showed no changes. There were a few lymphocytes and plasma cells around the medial and adventitial blood vessels.

**Lungs** The pleura was markedly thickened by fibrous tissue, congested blood vessels and by lymphocytic infiltration. The alveolar septa, many of which were broken, were thickened by dilated and congested capillaries, lymphocytic infiltration and connective tissue. The alveoli contained red blood cells, polymorphonuclear leukocytes, lymphocytes and mononuclear wandering cells. There were hemorrhages in the walls of the bronchioles and also lymphocytic infiltration.

**Liver** The capsule showed no changes. The efferent veins and sinusoids were markedly dilated and were filled with red blood cells. The adjacent liver cords were narrower than normal and the liver cells contained a few vacuoles and a slight amount of yellowish-brown pigment. The Kupffer cells also contained this pigment. There was a slight increase in connective tissue and lymphocytes in the portal areas.

**Spleen** The capsule was not altered. The malpighian corpuscles were normal in number and cellular content but were decreased in size. The sinusoids were dilated and their lining cells were prominent. There was an increase in the amount of fibrous tissue and the number of red blood cells in the pulp. The walls of the arteries and arterioles were slightly thickened.

**Pancreas** There was a slight increase in the interlobular and intralobular fat. The cells of the islets, ducts and acini showed no changes.

**Adrenal** The cortical and medullary cells were normal in appearance. The capsule was not altered.

**Kidney** The capsule showed no changes. There was a slight increase in fibrous tissue in the glomerular tufts. An occasional polymorphonuclear leukocyte was seen in the glomerular capillaries. A granular eosinophilic material was present in some of the tubules and in the glomerular space. Lymphocytes were present around the blood vessels in the cortex. The arteries and arterioles showed no changes.

**Prostate** The acini and ducts varied little in size and shape. The lining epithelial cells of the former were heaped up and formed papillary projections. The fibromuscular stroma showed no changes.

**Stomach** The mucosa was infiltrated with lymphocytes, polymorphonuclear leukocytes and a few plasma cells. The submucosa, muscularis and serosa were not altered.

*Anatomical Diagnosis.* Syphilitic aortitis, partial stenosis of coronary ostia, syphilitic aneurysm of ascending aorta, compression of pulmonary artery by aneurysm with narrowing of the lumen. Compression of left auricle by aneurysm. Hypertrophy and dilatation of right ventricle. Mural thrombus of right auricular appendage. Chronic passive congestion of liver and spleen. Congestion of lungs. Ascites. Cyanosis, marked. Pulmonary arteritis with overlying thrombus. Left auriculitis with overlying thrombus. Fibrosis of pericardium. Pulmonary emphysema bilateral. Fibrous pleural adhesions, right. Chronic gastritis. Diverticulosis of sigmoid colon.

## DISCUSSION

The patient presented the clinical picture of acute primary cor pulmonale as shown by the rapid onset of severe dyspnea, orthopnea and cyanosis, evidence of right heart failure with distended neck veins and hepatomegaly, accentuated P<sub>2</sub>, marked increase in venous pressure and markedly prolonged lesser circulation time. Evidence of left heart failure was absent. All the usual efforts used in treating heart failure were of no avail.

The etiology of the syndrome was a source of much discussion during life. Some felt that syphilitic aortitis was present because of the history of syphilis, dilated aorta on the roentgenogram and the diastolic murmur at the base transmitted along the left sternal border. However this explained inadequately



clinical course of acute cor pulmonale Others believed, because of the diastolic murmur at the apex, the accentuated  $P_2$  and the enlarged left auricle as seen by fluoroscopy, that the patient had rheumatic heart disease with disease of the mitral and aortic valves and perhaps a concomitant syphilitic aortitis It was difficult to account for the clinical picture on this basis, also, inasmuch as no signs of pulmonary congestion were ever noted until just before death, and the symptoms of the right heart failure were so severe and acute in onset.

It is difficult to explain the murmurs by the postmortem findings Apparently there was no insufficiency of the aortic valve The diastolic blowing murmur at the base and along the left sternal border may have been due to a relative insufficiency of the pulmonary valve from pulmonary hypertension, producing a Graham-Steele murmur. One can only conjecture as to the anatomical basis of the presystolic murmur at the apex However, the only pathological change in the left auricle was that due to the pressure upon it by the aneurysm

Several articles have appeared in the literature concerning the production of cor pulmonale by obstruction of the pulmonary artery by syphilitic aortic aneurysms Garvin and Siegel,<sup>1</sup> in 1939 reviewed the literature and reported three personally observed cases They stated that the usual result is rupture of the aneurysm into the pulmonary artery, but that rarely the aneurysm does not rupture but causes a stenosis of the pulmonary artery This results in a burden on the right side of the heart, resulting in hypertrophy and dilation of the right ventricle, the so-called cor pulmonale In their review, the aneurysm was located in the ascending arch of the aorta involving either the sinuses of Valsalva or the region just above the commissures, and bulged anteriorly and to the left, encroaching upon the pulmonary artery

No case of aortic aneurysm with encroachment upon both the pulmonary artery and left auricle could be found in the literature In the Glasgow Medical Journal of 1897,<sup>2</sup> a report is mentioned of the presentation of a heart containing two aneurysms, both arising above the aortic valve One aneurysm projected against the left auricle The case was that of a 38 year old woman who complained of severe symptoms of heart disease of 13 weeks' duration "There were signs of cardiac hypertrophy with V S and V. D murmurs heard most distinctly at the lower sternum"

### CONCLUSION

A case of aortic aneurysm with encroachment upon the pulmonary artery and left auricle resulting in cor pulmonale and signs of left auricular obstruction is presented with the postmortem examination

### BIBLIOGRAPHY

- 1 GARVIN, CURTIS F, and SIEGEL, MORTIMER L Cor pulmonale due to obstruction of the pulmonary artery by syphilitic aortic aneurysms, *Am Jr Med Sci*, 1939, cxcviii, 679
- 2 Glasgow Med Jr. 1897, xlviii, 120-128

The authors wish to thank Dr I Ogden Woodruff (Director of the First Medical Division, Bellevue Hospital) for his criticisms and suggestions in the preparation of this paper

## CASE REPORT OF DISSECTING ANEURYSM OF THE AORTA WITH CARDIAC TAMPONADE\*

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ALTHOUGH dissecting aneurysm of the aorta with cardiac tamponade is not so rare as to warrant reporting in itself, this case is reported to stress the evolution of certain electrocardiographic changes noted in seriatim which may be of considerable diagnostic value

### CASE REPORT

On the morning of September 29, 1942, a white male adult 50 years of age was admitted to the Station Hospital. He appeared critically ill and complained of agonizing pain in the mid chest, back of the neck, throat, teeth, and both arms to the fingertips.

The patient stated that while he was standing in the field the pain and a gasping type of respiration suddenly appeared simultaneously in the above mentioned areas.

His previous personal history revealed the usual childhood diseases, tonsillectomy, and herniotomy. Seven years prior to admission he suffered an injury to the neck in an automobile accident, at which time there was a questionable fracture of a cervical vertebra. He had been known to have had a mild to moderate elevation of blood pressure for several years.

The family history was non-contributory except that the mother died of cerebral hemorrhage.

Physical examination revealed a critically ill middle-aged male adult. He appeared to be well oriented and in a state of collapse. The face was flushed. The fingers and toes were cold and clammy. There was no cyanosis and no difference in temperature or pulse of the two upper and lower extremities. The respirations varied between 50 and 60 per minute and were shallow and labored. The heart rate was found to be slightly rapid, but the sounds were of normal intensity. The blood pressure was 150 mm Hg systolic and 90 mm diastolic in both arms. He was well nourished and developed. Height was 5 feet 9 inches.

**Progress** Soon after admission patient was given morphine sulphate,  $\frac{1}{2}$  grain by subcutaneous injection. It was thought initially that the patient was suffering from an acute myocardial infarction, but because of the character of the pain the possibility of a dissecting aneurysm of the aorta was considered. About one hour after admission, the heart sounds became distant and a gradually increasing number of ectopic beats made their appearance. The gasping respiration subsided, the rate coming down from 40 to 50 per minute to 16 to 20 per minute. Oxygen was administered intermittently through a BLB type oxygen mask. Some two hours later an electrocardiogram was taken. At that time only pain across the mid-thorax persisted and the patient stated that the character of this pain differed from the original but he could not describe in what way it differed. That afternoon a test dose of quinidine sulphate was given to start this drug because of the numerous ectopic beats and as prophylaxis against a possible ventricular fibrillation. The blood pressure during the day varied between 150 mm Hg systolic and 90 mm diastolic and 140 mm systolic and 90 mm diastolic. The number of ectopic beats lessened and the intensity of the heart sounds became normal. The following day there was much improvement in the general condition and the only complaint was a slight precordial and neck pain. Only an occasional ectopic beat was noted. No pericardial friction rub was heard. The pa-

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tient was placed on quinidine and aminophylline, grains 3 each three times daily. The electrocardiogram was interpreted as showing myocardial infarction (anterior). Detailed description of the tracings will be given later.

On the second hospital day patient was given pantopon,  $\frac{1}{2}$  grain, at 11:00 p m and 5 30 the following morning because of increased pain in the neck and upper back. The pulse had varied between 90 and 100 during the night. The blood pressure that day averaged 140 mm Hg systolic and 104 mm diastolic. The heart rate and rhythm were normal except that the  $A_2$  became accentuated. On the third day temperature was 101° F, pulse 108, regular and of good quality. Fine crepitant râles were heard over both bases. The heart showed no abnormal sounds. The following day the patient was entirely comfortable except for mild headache and the crepitant râles were heard occasionally over the left base. On the fourth day the patient was distinctly better, blood pressure remained about 140 mm Hg systolic and 90 mm diastolic. The lungs were clear and the heart appeared to be normal. On the fifth day a pericardial friction rub was heard, best over the mitral area. General condition was good. The friction rub disappeared on the following day and the blood pressure averaged 138 mm Hg systolic and 88 mm diastolic, with a pulse of 90. On the morning of the seventh day the patient suddenly became anxious and restless and a cold, clammy sweat covered his body. The pulse was faint and difficult to obtain, and the heart sounds were found to be distant but regular. There was a sudden reappearance of severe pain over the entire precordium and the patient rapidly went into shock. An hour later a definite pulsus alternans appeared. The blood pressure was not obtainable. The apex rate was 98 with frequent ectopic beats and an apical systolic murmur, and an audible precordial friction rub was heard. Moist râles appeared in both lung bases. The patient was given morphine sulphate,  $\frac{1}{4}$  grain, and oxygen was administered again. Soon after he was given 50 per cent glucose and aminophylline,  $3\frac{3}{4}$  grains intravenously. Within two or three hours occasional pulse beats could be obtained, the extremities became warm, and the color appeared normal in the extremities. Marked perspiration continued, blood pressure was 90 mm Hg systolic and 60 mm diastolic. Respirations were 50 per minute. Another electrocardiogram that was taken the same morning showed no evidence of block or ventricular fibrillation. During the day there was gradual improvement and that afternoon the blood pressure was 130 mm Hg systolic and 80 mm diastolic. During the night there was a sudden collapse of the blood pressure again with a rising respiratory rate. The heart sounds became irregular and the temperature gradually rose to 106.8° F per rectum. At that time the blood pressure was 90 mm Hg systolic and 60 mm diastolic and about three hours later had risen to 120 mm Hg systolic and 80 mm diastolic. His condition remained the same until the following morning when the patient suddenly coughed, went into collapse rapidly, and died soon after.

*Laboratory Data* Soon after admission the urine was found to be normal. The blood count revealed normal red blood count and hemoglobin 90 per cent. There was a slight leukocytosis with a polymorphonuclear increase to 84 per cent with no shift to the left. Blood non-protein nitrogen was 40 milligrams per 100 c c. The sedimentation rate (Cutler tube) was 10 mm in 60 minutes. On the fourth hospital day the sedimentation rate had risen to 42 mm in 60 minutes. Several urine examinations throughout the course of illness revealed no abnormalities except for a trace to 1 plus albumin and 8 to 10 leukocytes per high power field. The blood non-protein nitrogen on the third hospital day was 43 milligrams per 100 c c.

*Electrocardiographic Studies* (See tracings below.) The first tracing (first column on the left), about two hours after admission, showed a rate of 80 with a normal sinus rhythm. PR interval 0.15. P-waves, 0.1. QRS complexes 0.07. Deep  $S_2$ .  $T_1$  diphasic.  $T_2$  diminished amplitude.  $T_4$  inverted. Marked left axis deviation. Interpretation: It was thought that the T-wave changes in Leads I and IV suggested an early acute anterior myocardial infarction.

Electrocardiogram, fourth day of illness (middle column) Rate, 104 Sinus tachycardia PR interval 0.14 P-waves, 0.08 Splintered  $QS_3$  and elevated  $ST_1$  and  $ST_2$   $T_1$  diphasic to inverted  $T_2$  diphasic to inverted  $T_3$  diphasic  $T_4$  inverted Interpretation Changes diagnostic of anterior apical myocardial infarction or acute pericarditis

Electrocardiogram eighth and last day of illness (last column on right) Rate 110 Sinus tachycardia PR interval 0.16 P-waves, 0.11  $ST_2$  segment elevated Deep  $Q_3$  Low  $R_3$  Interpretation As compared with previous tracings, the upright  $T_1$ ,  $T_2$ , and  $T_4$  indicated a reversion toward normal

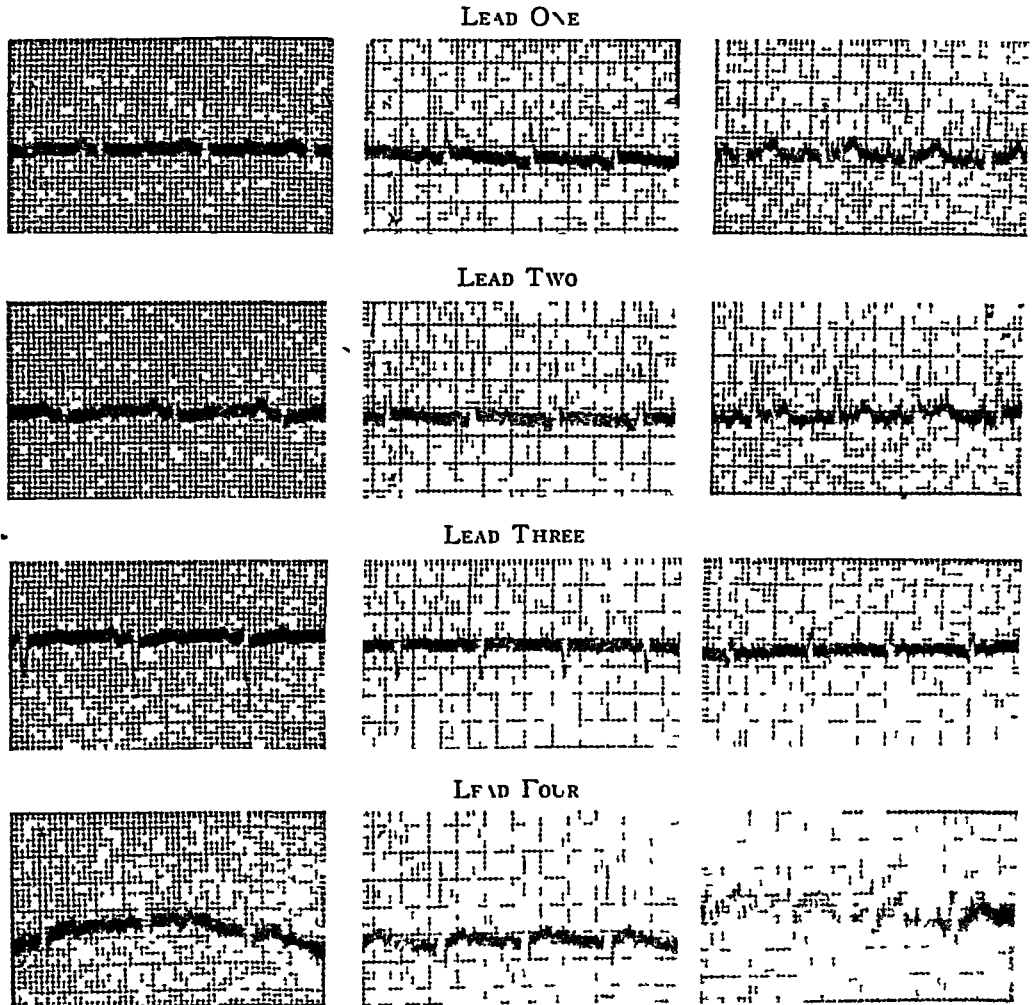


FIG 1

#### AUTOPSY PROTOCOL

*Pathological Diagnoses* 1 Hemorrhagic pericardial tamponade 2 Dissecting aneurysm ascending portion (intrapericardial) of the aorta 3 Sero-fibrinous and fibrinous pericarditis 4 Aorta—arteriosclerosis 5 Coronary artery—arteriosclerosis 6 Lungs—bilateral minimal pulmonary congestion 7 Kidneys—benign nephrosclerosis (early) 8 Liver—focal degenerative hepatitis 9 Brain—hyperemia (with diapedesis of red blood cells) of right parietal cortex

**Cardiovascular System** Gross findings of the cardiovascular system showed the pericardium to be quite distended. When it was opened, the parietal layer was found to be considerably thickened, measuring 0.3 cm. The pericardial sac was filled with free blood and cruor clot, representing a volume of approximately 500 cc. A serofibrinous exudate covered the right auricle, right ventricle, and extended on to the anterior surface of the left ventricle. This exposure showed the right auricle to be slightly distended and the right ventricle definitely more distended. The ascending portion of the aorta was seen to be larger than normal and measured 10 by 4 cm. The aorta was dissected free at the aortic hilus and then opened, after removal, along the greater curvature up to the aortic valve. This dissection showed that at a point 12 cm from the aortic sinuses there was a gradual thickening of the sheath about the adventitia up to a thickness of 2 cm. This circumscribed material covering that portion of the aorta was due to organizing extravasated blood. The examination of the intimal surface of the aorta showed a number of yellow atheromatous plaques, but no evidence of calcification in that region and no puckering and narrowing of the coronary orifices were noted. At a distance 3 cm above the left posterior aortic sinus there was a transverse rent in the aorta approximately 1.5 cm in length. The extravasated blood, confined within the sheath, extended far enough to cause possible compression externally upon the coronary orifices. The outer aspect of this dissecting aneurysm showed several circumscribed areas of organizing material, circular in arrangement, and up to 2 cm across and 3 cm in thickness. It was not possible to identify the point from which the blood had escaped through one of these areas into the pericardial sac. It is to be noted from the above that the entire dissecting aneurysm was intrapericardial. There was definitely no rupture of the heart itself.

After opening the right auricle, we found it to be intact. The right ventricle was ballooned out somewhat and was soft, red in color, and 0.7 cm in thickness. The left auricle was also intact and contained no thrombi in the appendages. The chordae tendineae and papillary muscles were normal. The endocardium was normal. The myocardium of the left ventricle was deep red and firm, measuring 1.5 cm at its greatest thickening. There was focal narrowing at the tip of the apex for a distance of 2 cm where the depth of the ventricle narrowed to 1 cm. This area was composed partly of white fibrous connective tissue which was in sharp contrast to the surrounding red myocardium. The aortic valve measured 8 cm across and was intact. Dissection of the right coronary and left coronary with its anterior ascending and circumflex branches showed the vessels to be patent throughout. In the first cm of the right and first 4-5 cm of the major branches of the left coronary there was evidence of atheromatous plaques but no calcification.

**Respiratory System** Right lung, 410 gm, left lung, 320 gm. Both lungs were somewhat similar in appearance, being grayish-black in color, with some reddening in both lower lobes. On cut section, they were pale gray, except in the lower lobes where there was deep reddening. No frothy or bloody fluid escaped. On opening the trachea and bronchi, particularly of the left side, there was abundant mucopurulent exudate which was quite tenacious but there was no evidence of dilatation of any of the bronchial passages. The peribronchial nodes were somewhat discrete and grayish-black in color.

**Bacteriological Examination** Culture of pericardial fluid showed no growth.

#### HISTOPATHOLOGY

**Parietal Pericardium** The section showed the pericardium to be thickened by hyalinized connective tissue and serofibrinous exudate. In the latter there were some large cellular structures, ovoid in shape, with lightly vesicular nuclei. These structures resembled hypertrophied endothelial cells, perhaps acting as macrophages. Occasionally a mitotic figure was present in them. **Diagnosis.** Serofibrinous pericarditis.

*Right Posterior Aortic Sinus* The intima and media were essentially intact, except for slight focal hyalinization, but again there was a thickening of the adventitia and surrounding sheath by granulation tissue and hemorrhagic exudate containing large numbers of polymorphonuclear leukocytes not seen in the previous section.

*Arch of Aorta* The section showed the intima to be essentially intact. The media showed a longitudinal area where the muscle fibers had become necrotic. There were red blood cells in this rent. The adventitia was continuous with a surrounding mass of granulation tissue. In the latter there was no perivascular round cell infiltration—in fact, no alteration in the vessels themselves. Further sections showed a small amount of lymphocytic deposition about a vasa-vasorum in the peripheral portion of the media and adventitia. In some of these sections, in addition to the granulation tissue, the outer part of the sheath showed the presence of homogeneous pink-staining material and red blood cells, with very little suggestion of iron pigmentation. Bacteria stains were negative.

Another section of aorta taken through a grossly atheromatous plaque showed the subintima and media to be irregularly thickened by hyalinization, replacing muscle fibers, and by fatty changes, together with cholesterol deposition. The central degenerative changes in the media in this section were somewhat similar to those seen in the portion taken directly from the dissecting aneurysm, except that in this section the cholesterol clefts were so apparent. **Diagnosis** Dissecting aneurysm and arteriosclerosis. An additional section showed a more recent extension of the process, with marked extravasation of sero-fibrinous material containing red blood cells and disintegrating leukocytes forming a very large mantle.

*Descending Aorta* **Diagnosis** Arteriosclerosis.

*Aperi, Left Ventricle* **Diagnosis** Sero-fibrinous pericarditis.

*Left Coronary* **Diagnosis** Arteriosclerosis.

*Bronchus, Left Lung* There was some hyperemia and hemorrhagic extravasation.

*Left Upper Lobe* Hyperemia.

*Right Lung, Lower Lobe* There was hyperemia of vessels and compression of many alveoli. **Diagnosis** Early passive congestion.

*Left Kidney* There was minimal thickening of the basement membrane of some of the glomeruli. The afferent arterioles appeared intact, whereas the interlobular arteries frequently showed subintimal hyalinization. Some of the proximal tubules contained pink-staining debris which was not from red blood cells. One of the branches of the renal artery showed early arteriosclerosis. **Diagnosis** Early benign nephrosclerosis.

*Liver* About the central veins there were present, in some instances, degenerating leukocytes but with some evidence of degeneration of hepatic cells in such areas. There was bile pigmentation. There was no fibrosis or proliferative activity. Occasionally, the leukocytic deposition was more extensive and more confined to the region of the central vein. Those areas of focal degeneration suggested early abscess formation. There was some scattered fatty infiltration. **Diagnosis** Focal degenerative hepatitis.

*Brain* Right parietal cortex showed hyperemia of the vascular channels with focal diapedesis of red blood cells. The latter often formed small mantles about those vascular channels with as then only very early necrosis of brain tissue. This focal lesion resembled the type so often seen in hypertensive individuals as reported by Chase. The larger vessels in the sulci were essentially normal. **Diagnosis** Hyperemia (with diapedesis of red blood cells).

The autopsy on this case was performed by Lt Col Stuart W Lippincott who added the following note on the pathogenesis of the pericarditis and dissecting aneurysm: "At the time of autopsy the size of the pericardium suggested the presence

of a tamponade, which was verified as soon as the pericardium was slit open. The thickness of the pericardium suggested that the pericarditis had existed for some time. On gross examination of the apex of the left ventricle, it was thought provisionally that an old, small myocardial infarct was present. However, this was not substantiated by microscopic section. Furthermore, the pericarditis was too diffuse to be accounted for by a small previous infarction. Cultures from the pericardial fluid were negative, helping to rule out a bacterial etiology. There was no indication that the pericarditis was associated with uremia. Examination and comparison of the pericardium and the intrapericardial dissecting aneurysm showed that in both there was evidence of recent hemorrhagic extravasation but that in addition there was old granulation tissue in both. It seemed, therefore, that the recent and old diffuse pericarditis was best explained as being associated with small recurrent extensions and leakage of the dissecting aneurysm, with organization until the final episode occurred, during which about 500 c.c. of blood escaped into the pericardial sac, death being due to the tamponade.

"The etiologic factor in the formation of the dissecting aneurysm was also of interest. In the region of the dissecting aneurysm there was very little evidence, grossly, of arteriosclerosis. For that reason other possible factors had to be considered. The age group that this man fitted into was considerably older than that usually associated with idiopathic medio-necrosis, but the man's aorta was small throughout for the size of his physique so that such an entity still remained as a possibility. Syphilis, disputed by most people as a possible factor in a dissecting aneurysm, was not present. Microscopically, periarteritis nodosa and a mycotic form of dissecting aneurysm were ruled out. Finally, microscopically, in the dissecting aneurysm, wide subintimal and medial evidence of arteriosclerosis was found and was directly associated with the formation of the lesion."

The evolution of the electrocardiographic changes worthy of note in this case were that on the first tracing soon after admission the patient showed  $T_1$  and  $T_4$  inversion with upward convexity of  $ST_4$  suggesting an acute early anterior myocardial infarction. Three days later it will be noted that the further changes of  $T_1$  and  $T_4$ , especially as compared with the first tracing, are diagnostic of anterior apical myocardial infarction. The last tracing, taken on the day prior to death when the signs and symptoms of severe cardiovascular collapse appeared, showed a reversion toward a normal tracing.

In studying this series of electrocardiographic films in relation to the autopsy findings, the following speculations seem reasonable. During the early phase of the patient's clinical course in which the chest pains were prominent, there was a bulging of the root of the aorta due to displacement by the subintimal hemorrhages so that narrowing of the coronary ostia could occur. When the last electrocardiograph was taken a few hours prior to death, presumably the further destructive processes of the dissection which eventuated in the out-pouring of blood into the pericardial sac caused a release of this contiguous pressure and again allowed an adequate patency of the previously compressed coronary artery. The drop in blood pressure probably played a part as well.

Although this is purely speculative, it seems to be a reasonable explanation of the changing electrocardiographic findings from that of coronary occlusion at the onset of the illness to what appeared to be an almost normal tracing only eight or nine days later.

Certainly if one should encounter an individual showing evidence of either dissecting aneurysm of the aorta or acute myocardial infarction clinically, such a series of electrocardiographic tracings would be of considerable diagnostic aid in the differentiation of the two entities.

## SPLENIC NEUTROPENIA REPORT OF A CASE WITH SPLENECTOMY<sup>\*</sup>

By WANN LANGSTON, M D, F A C P, O A WHITE, M D, and J D ASHLEY, Jr, Lt, M C, A U S, *Oklahoma City, Oklahoma*

IN 1939 Wiseman and Doan<sup>1</sup> described a new syndrome closely related to congenital hemolytic icterus and essential thrombocytopenic purpura. The chief features of this condition are splenic enlargement accompanied by an absolute neutropenia in the peripheral blood. The neutropenia is relieved by splenectomy. These authors presented three cases in 1939 and five additional cases in 1942.<sup>2</sup> Moore and Bierbaum reported a similar case in 1939,<sup>3</sup> and Muether, Moore, Steward and Brown recorded another in 1941.<sup>4</sup> The purpose of this paper is to present one additional case also treated with splenectomy with favorable response.

### CASE REPORT

The patient, T H, is a 56-year-old white male pharmacist who was first seen in the plastic surgery clinic of the University Hospitals on October 1, 1942, because of a scar tissue contracture in the left popliteal space which prevented extension of the leg to more than 150 degrees. The patient had suffered from atrophic arthritis for about six years, and two years previously had fallen and sustained a deep laceration on the upper part of the calf which had healed very slowly leaving the scar. In the preliminary work-up, the white blood cell count was observed to be 1800 with 78 per cent lymphocytes and 22 per cent polymorphonuclear cells. Further questioning revealed that the patient had taken (estimated) 400 five grain tablets of sulfamidamide during the period of healing and from 100 to 150 grains of aspirin weekly, as well as unknown quantities of phenacetin. This medication was taken because of the moderately severe atrophic arthritis which involved the knees, back, shoulders, wrist, hands and neck. In 1938 while the leg ulceration was healing a white cell count was recorded as 2,400. His previous physician had placed him on yellow bone marrow of which he took about 100 capsules, because of the neutropenia. Later liver extract was given over a period of one year with no increase in white blood cell count.

He was advised to discontinue all medication and return for checks on the white blood cell count. On October 17 the red blood cell count was 5,200,000 with 18 grams of hemoglobin, the white blood cell count was 1,700 with 73 per cent lymphocytes, 14 per cent young neutrophils, 4 per cent band forms, 2 per cent eosinophiles, 1 per cent basophiles and 10 per cent monocytes. On November 17 the white blood cell count was 1,400 and no neutrophils were seen in the blood film. A sternal marrow biopsy which was taken at the same time revealed 29 per cent myelocytes, 12 per cent juvenile neutrophils, 25 per cent mature neutrophils, 4 per cent eosinophiles, 1 per cent basophiles, 26 per cent lymphocytes and 23 per cent nucleated red blood cells.

The presence of a normal bone marrow picture in the face of the marked neutropenia in the peripheral blood was confusing so the patient was admitted to the hospital on November 25 for more complete study. No complaints were present other than the disability from the leg contracture and arthritic deformities of the feet and wrists. The arthritis had been inactive for at least one year. The family history was negative for any type of blood dyscrasia. The past history was negative for chronic disease of any type except malaria during childhood which had been asymptomatic.

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tomatic for at least 30 years. He had a tonsillectomy in 1937 with uneventful recovery. No record was made of the blood picture at that time.

Physical examination revealed a well developed, somewhat undernourished, white male who looked slightly older than the stated age. There was a faint tremor of the hands resembling that found in Parkinsonism and the facial expression was slightly mask-like. The skin was dry and scaly over the exposed areas. The eye-grounds were negative. The mouth was edentulous. The chest was clear throughout. The pulse rate was 80 with a regular rhythm. The blood pressure was 120 mm Hg systolic and 80 mm diastolic. There were no cardiac abnormalities. There was no tenderness in the abdomen. The spleen was palpable as a large, firm, movable mass, extending 6 cm below the costal margin. The splenic notches were discernible. Over the left popliteal space was a scar measuring 12 by 4 cm which held the joint so that extension was limited to 150 degrees.

The complete serial laboratory studies are given in the accompanying table. Because of the triad of arthritis, splenomegaly and leukopenia, the impression was gained that the patient was suffering from "Felty's syndrome." However, in the face of a

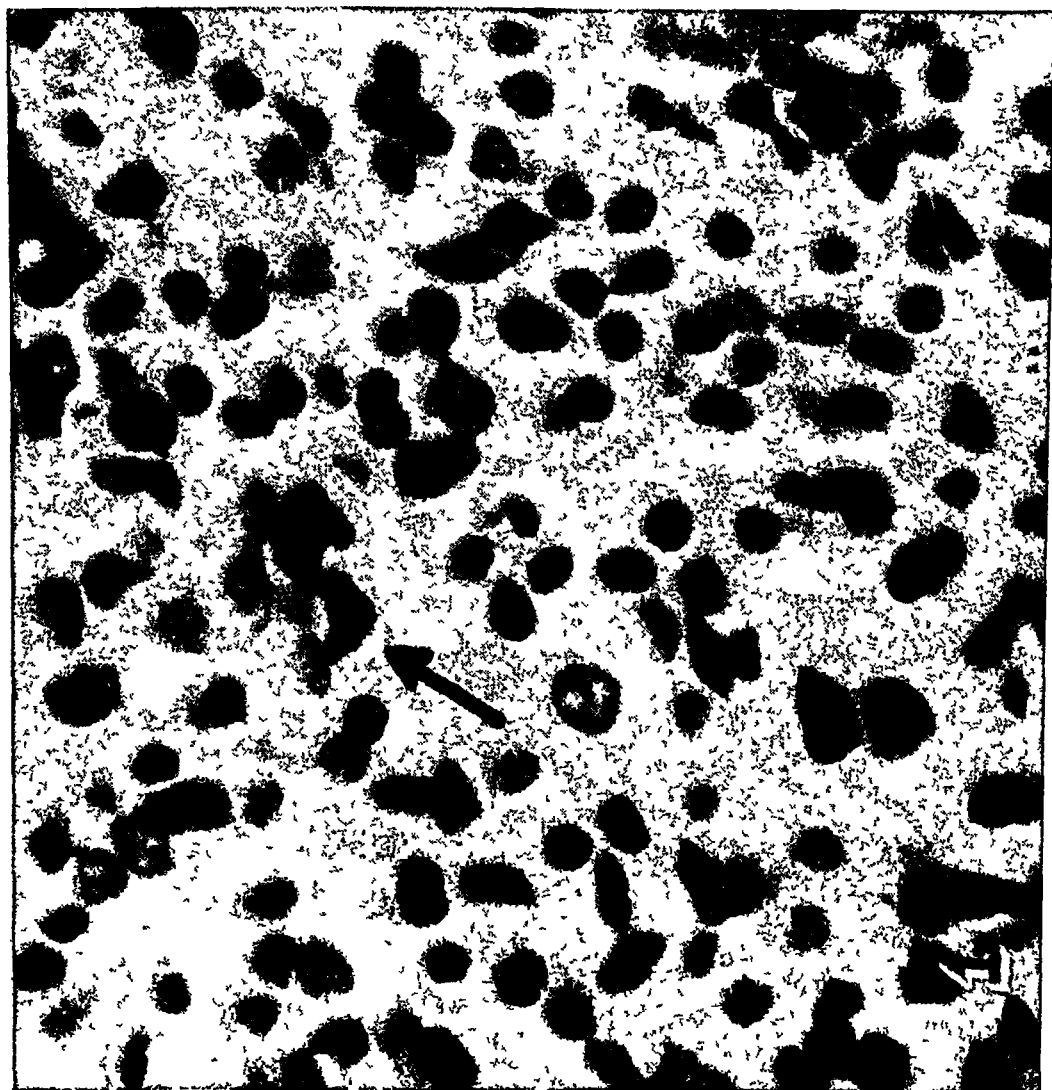


FIG. 1. Photomicrograph from paraffin section of spleen showing a phagocytic cell containing fragments of polymorphonuclear cells. Hematoxylin-eosin stain. Approximately  $\times 1,000$ .

slightly increased icteric index, a mild degree of polycythemia, a normal platelet count and high normal reticulocyte count, it was suggested by one of us (W L) that this picture more closely resembled the primary splenomegalic neutropenia described by Wiseman and Doan

On December 10 retrograde pyelography was done to demonstrate that the mass felt in the abdomen was not renal in origin. The left kidney was visualized as in the usual position and unrelated to the mass. On December 11, 1942, a splenectomy was done under general anesthesia by Dr O A White. It was noted that the spleen was about four times the usual size with a thickened capsule and several small areas of white discoloration of the surface indicating a perisplenitis. There were no adhesions to the peritoneum or neighboring organs. The spleen weighed 720 grams. The gall-bladder contained one stone but was not removed.

Microscopic examination of the spleen revealed the capsule and septa to be fairly broad. Malpighian corpuscles were well developed and located at some distance from one another. There was some increase of the connective tissue stroma in the pulp. The capillaries in the pulp were filled with red blood cells and a number of granulocytes and their precursors. These were more numerous than normal in many areas. Definite phagocytosis of polymorphonuclear cells could be seen in the fixed tissue (figure 1). The pathological examination was done by Dr Bela Halpert.

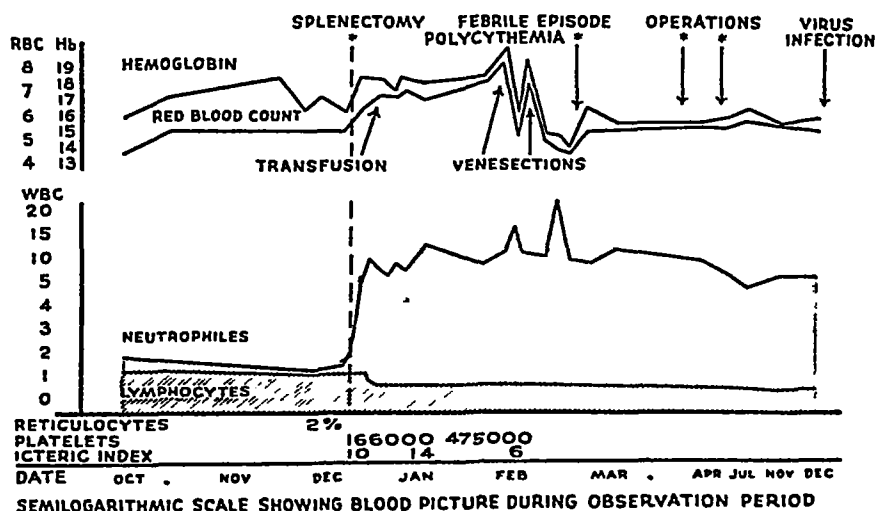


FIG 2.

The postoperative course was uneventful except for a prompt rise in neutrophils in the peripheral blood. The pre-operative white blood cell count was 2,800. In 12 hours the count had risen to 6,750 with 60 per cent neutrophils. The preoperative platelet count was 166,050. Five hundred cubic centimeters of bank blood were given shortly after the operation. On December 14 the white blood cell count was 11,700 with 70 per cent neutrophils. The blood picture is given in the accompanying table in serial form. On December 17 the icteric index was 14, though no clinical jaundice was visible.

The patient was discharged on January 5 with the wound completely healed. The white blood cell count was 14,600 with 63 per cent neutrophils, 4 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes, 7 per cent monocytes. The red blood cell count was 6,000,000, hemoglobin 17.6 grams. The platelets numbered 475,000.

Two weeks later on January 19, 1943, the patient returned to the Emergency Room

complaining of a severe headache and was obviously plethoric. He had had a chill 24 hours before and fever of  $103^{\circ}$  lasting two hours. The red blood cell count was 6,900,000 with 18 grams hemoglobin. A venesection was done and 500 c c blood were removed, which resulted in prompt relief of the headache. One week later the red blood count was 8,000,000 with 19.5 grams of hemoglobin. The headache had returned. The venesection was repeated and was again followed by relief. On January 31, 1943, he again suffered a severe chill with a fever of  $104^{\circ}$  and a pain in the left epigastrium. This series of chills with fever rise to  $103^{\circ}$  or  $104^{\circ}$  recurred daily and on February 2, 1943, he was re-admitted to the hospital. The pain later became localized in the left costovertebral angle.

The only physical finding of note was several small punctate hemorrhages of recent origin in the left retina. The red blood cell count was 5,500,000. Blood cultures and repeated examinations of the blood for malaria were negative. Nevertheless, 30 grains of quinine sulfate were given daily for 10 days because of the history of childhood malaria. Roentgen-ray examination revealed a thickened interlobar pleura on the left and obliteration of the left costophrenic angle. Cystoscopic examination with urinalysis of ureteral urine failed to reveal presence of infection. The daily white blood cell count during this febrile period ranged from 12,000 to 22,000.

By February 24, 1943, all symptoms had cleared up and though the etiology of the febrile disturbance was undetermined, it demonstrated that the usual neutrophile response to febrile infection was obtained.

On March 5, 1943, the scar tissue in the left popliteal space was excised and a split graft utilized to repair the defect. The leg was placed in full extension. On April 13, 1943, one small additional granulating area at the edge of the original graft was covered with pinch grafts. This healed uneventfully. On May 7, 1943, patient was discharged after intensive physical therapy designed to promote motion in the leg. The red blood cell count was 5,300,000 with 16 grams of hemoglobin. The white blood cell count was 9,400 with 68 per cent neutrophils and 32 per cent lymphocytes.

The patient remained in good health and returned to his previous position as a pharmacist. In September and October, 1943, he was seen several times because of a contact dermatitis which proved to be due to laundry soap.

On November 14, 1943, a red blood cell count was 5,500,000 with 16 grams of hemoglobin. The white blood cell count was 7,250 with 75 per cent neutrophils and 25 per cent lymphocytes.

He was readmitted on December 20, 1943, because of an acute tracheobronchitis, presumed to be of virus origin. This produced a fever of  $100^{\circ}$  on admission. The red blood cell count was 4,800,000 with 15.6 grams of hemoglobin. The white blood cell count was 8,600 with 55 per cent neutrophils, 4 per cent eosinophils, 1 per cent juveniles, 1 per cent basophils, 34 per cent lymphocytes, 3 per cent monocytes. Spontaneous recovery occurred in four days.

The patient's arthritis improved symptomatically so that at the time of this report there were no symptoms other than residual deformities produced during the active phase. He was working full time.

## DISCUSSION

In 1933 Turley demonstrated that phagocytosis or perhaps extracellular enzymatic destruction of polymorphonuclear cells occurs in the spleen from a study of impression preparations of fresh splenic material, though the clinical significance of this was not recognized until some time later. He suggested that a hitherto unrecognized function of the spleen was disposal of polymorphonuclear cells in the normal individual. It was not until 1939 that the first published re-

ports of a clinical splenic neutropenia verified this function of the spleen. In this report, Wiseman and Doan postulated that the mechanism of production of the neutropenia was the excessive phagocytosis of neutrophils by the clasmatoocytes in the spleen. This process was considered an exaggeration of the phenomenon which occurs in the normal spleen. The removal of dead, effete or "senile" neutrophils by the spleen is compared to the well recognized destruction of aging erythrocytes by the same organ. In several of their cases parallel phenomena of thrombocytopenia and hemolytic anemia were present, suggesting that the spleen itself had undergone a change in degree of activity so that not only the formed elements which had outlived their normal life span were destroyed, but also mature functional elements.

In the splenic neutropenia of severe degree practically all of the neutrophils are destroyed. The presence of a normal or hyperfunctioning bone marrow is explained on the basis that it is not involved directly, instead the hematopoietic system is constantly attempting to regenerate cells in an effort to maintain the usual number in the peripheral blood stream.

"Feltz's syndrome" of leukopenia, splenomegaly and atrophic arthritis resembles splenic neutropenia at least in the superficial features. This somewhat vague symptom complex has been questioned by Talkov et al.<sup>5</sup> as in many cases an atrophic arthritis is actually only a concomitant finding in various types of splenomegaly. It is of interest that two of Wiseman and Doan's cases and the present case had arthritic symptoms.

Splenic neutropenia is frequently precipitated by infection, or at least the clinical and hematological features become apparent during or following infections. One may equally suggest that the neutropenic individual is more susceptible to chance infection and that the infection merely calls attention to a hitherto unsuspected neutrophil deficiency.

The diagnostic criteria as laid down by Wiseman and Doan are

A Clinical—

- 1 Splenomegaly
- 2 Occasional purpura (thrombocytopenia)
- 3 Occasional oral ulceration (neutropenia)
- 4 Icterus, mild (hemolysis)

B Hematological—

- 1 Bone marrow
  - a Hyperplastic for myeloid series
  - b No abnormal cells
  - c Not leukemic
- 2 Blood
  - a Marked specific neutropenia
  - b Anemia (macrocytic, hyperchromic)
  - c Reticulocytosis
  - d Increased serum bilirubin (depending on degree of anemia)
  - e Thrombocytopenia (variable)

(For a more comprehensive understanding, the reader is referred to their original description<sup>2</sup>)

## COMMENT

This case has all the above features. Moreover this patient presented almost a "pure" splenic neutropenia, in which thrombocytopenia and anemia were practically absent, though a marked platelet rise as well as a transient polycythemia followed splenectomy. This suggests that some destruction of these elements was occurring but a compensatory hyperfunction of the myeloid tissue had managed to keep the platelet and erythrocyte count up to the physiologically normal level. The hyperfunction then continued for a period of about one month after splenectomy and subsided slowly.

The popliteal space infection corresponds well to the occasional oral ulcerations noted in other patients, in this individual careful oral hygiene and absence of natural teeth had probably prevented such complication. The postoperative infection, though not identified, resulted in a prompt neutrophile increase, demonstrating that the bone marrow was capable of a normal response to what may be presumed to be a pyogenic stimulus. A virus type of tracheobronchitis one year later did not result in leukocytosis.

A gradual improvement in the arthritis with disappearance of symptoms except for deformities produced during the acute stage further suggests that the arthritis may have been a sequel of the neutropenia. The rôle of this patient's childhood malaria in production of splenic overactivity is obscure.

## SUMMARY

A case of chronic splenic neutropenia is presented in a 56-year-old white male. Attention was called to the disease by routine blood studies preparatory to plastic surgery. The neutropenia was dramatically relieved by splenectomy. This was followed by a prompt rise in neutrophiles, platelets and erythrocytes in the peripheral blood. The syndrome was associated with atrophic arthritis.

*Follow Up Report* Sep 15, 1945. This man reports feeling exceptionally well, has missed no time from work, has no fatigue. Blood Count Hb 15.5 gm, RBC 5,880,000, WBC 11,700, N 59 per cent. Blood chemistry within normal range. Urinalysis negative.

## BIBLIOGRAPHY

- 1 CRAVENS, E. B., JR. Splenectomy in chronic arthritis associated with splenomegaly and leukopenia, *Jr Am Med Assoc*, 1934, cii, 823-826
- 2 DOAN, C. A., and WISEMAN, B. K. Primary splenic neutropenia, *Ann Int Med*, 1942, xvi, 1097
- 3 MOORE, C. V., and BIERBAUM, O. S. Chronic neutropenia treated by splenectomy, *Internat Clin*, 1939, iii, 85-95
- 4 MUETHER, R. O., MOORE, O. T., STEWARD, I. W., and BROWN, G. O. Chronic granulocytopenia caused by excessive splenic lysis of granulocytes, *Jr Am Med Assoc*, 1941, cxvi, 2255-2257
- 5 TALKOV, R. H., BAUER, W. and SHORT, C. L. Rheumatoid arthritis, splenomegaly and leukopenia, *New England Jr Med*, 1942, ccxxvii, 395-398
- 6 TURLEY, L. A. A study of the spleen in various diseases by new methods preliminary report, *South Med Jr*, 1933, xxvi, 863-869
- 7 WISEMAN, B. K., and DOAN, C. A. A newly recognized granulopenic syndrome caused by excessive splenic leucolysis and successfully treated by splenectomy, *Jr Clin Invest*, 1939, xviii, 473

## A SYNDROME TERMED REITER'S DISEASE (URETHRITIS, CONJUNCTIVITIS AND ARTHRITIS) \*

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ALTHOUGH in the older German literature there were several cases suggestive of "Reiter's disease," it was not recognized as a clinical entity until 1916 when Reiter<sup>1</sup> described a clinical picture of urethritis, conjunctivitis, and arthritis which was non-gonorrheal in nature, therefore, credit must be given him for being the first one to recognize this "disease" and its symptomatology

During World War I, Reiter observed the syndrome in a young officer who had become suddenly ill with abdominal pains and diarrhea which showed a slight admixture of blood. Two days after the onset a purulent urethral discharge developed, accompanied by a suppurative conjunctivitis and acute arthritis of the right knee. No gonococci could be demonstrated in the urethral and conjunctival discharges. The existing urethritis slowly improved without any local treatment, but three weeks after the onset there was an extension of the arthritis to the left ankle, right elbow and left wrist. The urethritis and conjunctivitis had disappeared by this time, but the patient suffered constantly from severe joint symptoms. The temperature varied for weeks between normal and 102.2° F, being higher in the evenings. Two months later there was an exacerbation of the conjunctivitis and this was soon followed by swelling of the prepuce and a marked cystitis. After the patient had been confined to bed for 10 weeks, his general condition showed gradual improvement. During the course of the patient's illness, Reiter was able to demonstrate a spirochete in the blood. Because of the peculiar boring movements of the organism in the dark field preparations, it was designated by him as "*Spirochaeta forans*." The organism differed from the pallida in that it was easily stained with methylene blue and diluted fuchsin solutions. The spirochete was non-pathogenic for guinea pigs, but mice perished in eight days with an enormous excretion of sweat. However, no spirochete could be demonstrated in the blood or organs of these animals.

On the basis of finding spirochetes in the blood of his patient, Reiter proposed the name of "*Spirochaetosis arthritica*" for this disease. Since that time no one has been able to demonstrate such an organism with the procedure set forth by Reiter. Until further investigation establishes a definite etiologic factor, it is better to call this a syndrome rather than a disease.

In succeeding years most of the cases reported have been in Germany. At the present writing there are approximately 65 cases reported in the literature, most of them originating in Europe. Pioneer work in the United States was done by Bauer and associates<sup>2</sup> at Massachusetts General Hospital, where in 1942 they reported six cases considered to be typical of this syndrome. Further studies are being done by these workers at the present time.<sup>3</sup>

The urologist is perhaps the first to encounter patients with this symptom-complex, because the initial symptoms are frequently related to the genitourinary tract. However, this condition is a problem not only for the urologist, but other clinicians as well. Reviewing some of our previous clinical records with other

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diagnoses, we believe that with our present knowledge of this disease, a few of them might have easily been classified as cases of the syndrome Reiter's disease. We are certain that there are many cases throughout the nation resembling this condition, but they have been inadequately or improperly diagnosed, either because of inadequate facilities or non-acquaintance with this syndrome. Most often these patients have been treated for a non-specific urethritis, acute conjunctivitis (including "pink eye") or "acute rheumatism."

Although we have only two clinical abstracts to present at this time, they illustrate the syndrome of Reiter's disease along with some of the more severe manifestations.

### CASE REPORTS

*Case 1 Present Illness* A 30 year old white male was admitted to the hospital with the chief complaints of urethral discharge, mild joint pains, and smarting of the eyes. The following history was obtained:

At the age of 15 he was suddenly stricken with marked hematuria, a high fever and mild joint pains. In a few days a whitish to yellow urethral discharge appeared. At that time large blood clots were passed during urination with considerable pain in the urethra. A few days later a profuse purulent conjunctivitis developed with accompanying pain and photophobia. He was treated for cystitis, pyelitis and conjunctivitis. The symptoms subsided in about a month. Later a cystoscopy revealed a markedly injected bladder. All smears and cultures for organisms were apparently negative. The prostate was massaged bi-weekly for about one month because of slight enlargement. He had no further symptoms and changeable weather had no effect on his joints.

Four years later the patient again had symptoms of urethritis, cystitis, mild arthritic pains with slight swelling and conjunctivitis. He states that he had a fever of about 101° F to 103° F daily accompanied by pain across the lumbar areas and also an occasional chill lasting for only a few minutes. Dysuria and hematuria were present during the first few days of the attack. All laboratory tests were apparently negative again except for the blood and pus in the urine. The diagnosis of pyelitis with secondary cystitis and prostatitis was again made. The eye and joint symptoms subsided in a few days, and the patient was apparently well three weeks after the initial symptoms had appeared. No history of sexual exposure had been present. Shortly thereafter the patient was married, but marital relations had no effect upon his condition and there was no evidence of any pelvic or urinary disease in the wife. About six months later the patient again had similar symptoms for only a few days which quickly subsided with bed rest.

In August 1937, the patient stated that he was suddenly awakened by pain and swelling of the left elbow followed in 24 to 48 hours by extension to the right and left knee joints. The joints were "so painful that even a bed sheet could not be tolerated over them." This time the joints became markedly swollen with a massive effusion but there was only slight redness. In a few days a marked hematuria and urethral discharge of thick pus accompanied by a severe purulent conjunctivitis appeared. All smears for gonococci were negative. All cultures, blood serologic tests, agglutination, and complement-fixation reactions were negative. A non-hemolytic streptococcus was obtained from the blood but was later thought to be a contaminant when subsequent cultures failed. The patient remained in bed for two months and convalesced for another two months. During the course of his illness he had several mild chills with the temperature reaching 104° to 105° F. He was extremely toxic and even though the tentative diagnosis of pyelitis and cystitis with possible septicemia was made, the urologist was not satisfied with the diagnosis. Neo-

prontosil was administered but with no apparent effect. Absolute bed rest seemed to be the only helpful treatment. There were no residual joint symptoms. Prostatic massage was instituted after the acute phase of the illness had subsided. Later a cystoscopy revealed injection of the mucosa of the bladder but no disease of the kidneys was demonstrated. *E coli* was cultured from the urine. No further symptoms were present and the urine had been normal on frequent examinations until the present illness.

Six months prior to this report the patient was seen as an out-patient when he began to have a slight whitish urethral discharge accompanied by burning and frequency. The urine 3 glass test showed cloudy sediment composed of many pus cells in the first two, but the urine sediment in the third glass revealed a few pus cells. The prostate was slightly boggy and tender, and the right seminal vesicle was apparently blocked. Prostatic smears after massage revealed many pus cells and diminished lecithin bodies. Sulfonamides had no effect on the course of the disease. It was felt at the time that most of the trouble was caused by the prostate, so bi-weekly massage plus diathermy daily to the perineum were started. Relief was obtained for a short time, but then the patient had mild arthritic pains and occasional urethral discharge. The conjunctivae were injected and a small amount of sero-purulent material could be obtained. Smears failed to show any pathogens. He continued on duty until October 1944, at which time improvement was noted while on leave. After he returned to duty his symptoms recurred. On three occasions there was hematuria. Having lost 35 pounds of weight in six months, the patient was hospitalized for further study and treatment.

**Personal and Family Histories** These were essentially negative.

**Physical Findings** Normal findings were present except for the following: a moderate conjunctivitis and episcleritis of both eyes, profuse purulent urethral discharge, tenderness and swelling of the metacarpo-phalangeal joint of right index finger, mild tenderness but no swelling of both knees. Temperature 37.2° C, pulse 90, respirations 18.

**Laboratory Data** Repeated smears of urethral discharge showed many pus cells with occasional gram-positive cocci. Prostatic smears (wet) revealed many pus cells and a few lecithin bodies but no bacteria. Smears of the conjunctival secretion revealed gram-positive cocci, some in short chains and others in clusters. Cultures of the eyes showed a few diphtheroid colonies and *Staphylococcus albus*, the latter being non-pathogenic on the basis of the coagulase test. The cultures of the urethral and prostatic secretions were negative except on two occasions when *E coli* and *Staphylococcus albus* were grown. Repeated cultures of the urine failed to reveal any pathogens. All animal inoculations, including those for tuberculosis, failed to provide any new evidence. Blood films and cultures were negative. Scrapings of the urethra and conjunctivae were negative for inclusion bodies. Blood studies revealed Red blood cell count 4,400,000 to 5,000,000 and white blood cell count 10,500 to 13,200 with a slight increase in the polymorphonuclear cells. Hemoglobin ranged from 85 per cent to 95 per cent. The sedimentation rates varied from a high of 18 mm per hour to 12 mm per hour and at the time of discharge from the hospital they had returned to normal. The uric acid and non-protein-nitrogen were within normal limits. Blood Eagle and Mazzini reactions, repeated complement-fixation tests for gonorrhea, and agglutination for typhoid, dysentery and Brucella groups were negative.

Repeated urinalyses showed Specific gravity 1.008 to 1.022, acid reaction, trace to one plus albumin, occasional to frequent red blood cells, few to clumps of pus cells, no casts, and some mucous shreds and epithelial cells. Dark field examinations, Giemsa and methylene blue stains failed to show any spirochetes in the urethral discharges.



Additional Studies Frei, Ducrey, and intradermal allergy tests were negative. The electrocardiogram was normal. Roentgenograms of the teeth, paranasal sinuses and chest were normal. No evidence of a focus of infection was found. Roentgenograms of the joints and long bones revealed no pathological change. All renal function tests, including intravenous pyelograms, were normal. Stool culture for pathogens was negative.

**Course and Treatment** While in the hospital the patient was given a régime of complete bed rest, penicillin 20,000 Oxford units every 2 hours for 35 doses combined with sulfathiazole grams 1 every four hours and a nutritious diet. The symptoms subsided slowly and a prolonged convalescence of two months was prescribed after the patient was discharged. Apparently chemotherapy had very little if any effect on the course of the disease. Bed rest seemed to be the only positive therapeutic measure. Specimens have been sent to the National Institute of Health for further studies and virus determination. The results may not be known for several months.

**Case 2 Present Illness** A 21 year old white male was admitted to the outpatient department complaining of pain in the back and a discharge from the penis of 24 hours' duration. A history of sexual contact during September 1944 on several occasions was obtained, the last exposure having been one day prior to admission.

The urethral discharge was mucopurulent in character and the pain was located in the left lumbar region and radiated around to the left abdomen but not into the testis or penis. The pain was intermittent in character and was unaccompanied by other symptoms. No history of hematuria or dysuria was obtained at that time.

**Personal and Family Histories** The patient's last tropical service was in September 1943 in the West Indies but no history of any illness while serving in that region was obtained. The patient denied any previous venereal disease. At the age of six years he suffered from pneumonia and an appendectomy was performed during the same year. The family history was negative.

**Physical Findings** Examination was essentially normal except for evidence of tenderness in the left lumbar area and a mucopurulent urethral discharge. The prostate was normal in consistency, shape and size.

**Laboratory Data** Stained smears of the urethral discharge revealed occasional gram-positive cocci and a moderate number of pus cells. No gram-negative organisms were noted. Chocolate-agar cultures were negative for gonococci.

**Treatment** This consisted of 125,000 Oxford units of penicillin, and owing to the patient's required presence in Texas, he was not given further treatment at that time.

**Subsequent Course** The penicillin had no effect on his urethritis. The discharge became more profuse and the lumbar pain became more severe. He was admitted to another hospital on October 24, 1944. The diagnosis of pyelitis was made and the cultures of the urine and discharge failed to show any evidence of gonococci. Some cultures revealed gram-positive diplococci. Sulfathiazole was administered but because of the presence of a hematuria after one week of the drug, the sulfonamide was discontinued. However, the urethral discharge became more profuse. The patient was given 150,000 units of penicillin intramuscularly and the discharge subsided but the hematuria persisted. There was pus in all three glasses of urine. Cystoscopy was performed late in November 1944 at which time there was a marked hemorrhagic cystitis. The urine from both ureters was clear and free from pus. The patient developed an excoriation on the glans penis on November 8, 1944, which persisted after his discharge from the hospital in Texas. Dark field examinations and blood serologic reactions were negative for evidence of syphilis. The urethral discharge ceased on December 16, 1944.

While returning to New York the patient became ill aboard the train and was hospitalized at the U S Marine Hospital, Cleveland, Ohio, on December 23, 1944, complaining of severe pain in the back and reappearance of the urethritis.

**Course During Last Admission** The physical and laboratory findings on admission were essentially those of previous studies. Repeated cultures failed to establish an etiologic agent. The patient had lost 22 pounds in weight in six weeks. The urine 3 glass test showed a small amount of pus in each glass on repeated examinations during December 1944 and January 1945. The discharge and back pain ceased January 16, 1945. Intravenous pyelography on admission revealed a dilated left kidney pelvis but in January 1945 a normal pyelogram was obtained. Repeated complement-fixation tests for gonococci and the dysentery groups were negative. Blood cultures failed to reveal any pathogens. Repeated inoculations in guinea pigs showed only *E. coli*. On February 2, 1945, there was marked cloudiness of the urine in all three glasses and pus cells were numerous on microscopic examination. A marked dysuria and urethral discharge developed February 3 and these were followed by a terminal hematuria beginning February 6. There was marked tenesmus at terminal urination with the passage of large blood clots, after which the patient was relieved. Morphine was required to give relief at frequent intervals.

The hematuria persisted and on February 14 a severe bilateral conjunctivitis developed. Four days later the patient complained of marked pain and swelling of both knee joints. On February 22 the hematuria and urethral discharge ceased, but the conjunctivitis and the arthritis remained. In three days there was swelling and mild redness of the right wrist joint. Salicylates had no effect on the course of the joint symptoms. All symptoms subsided gradually and there were no sequelae at the time of discharge on April 17, 1945.

**Summary of Laboratory Data** The urine studies revealed a range from many pus and red cells during the illness to normal findings at the time of discharge from the hospital. Cultures of the urine showed occasional colonies of *E. coli* but no other bacteria.

Cultures of the blood, conjunctivae, urethra and joint fluids were all negative for pathogens. Guinea pig inoculations were negative except for recovery of *E. coli* in several of the animals.

Scrapings of the conjunctivae were sent to the National Institute of Health, Bethesda, Maryland. The report is as follows: "Diagnosis: chronic conjunctivitis, cause undetermined. The conjunctival scrapings are focally covered by a thin layer of stratified squamous epithelium. The corium consists of a loosely textured fibrous tissue irregularly infiltrated by lymphocytes, some larger mononuclear cells, and occasional polymorphonuclears. No possible etiologic agents or inclusion bodies were identified."

The sedimentation rates remained high. They ranged from 25 mm per hour to 20 mm per hour.

Roentgenogram of the chest revealed normal findings. Roentgenograms of the bones failed to show any pathological process.

Blood counts performed at frequent intervals showed red blood cells 4.4 to 5 million, leukocytes 13,300 to 6,450, hemoglobin 80 to 95 per cent and normal differential counts. The blood picture was normal at time of discharge from the hospital. There was a wide variation in the prothrombin time. At the hematuria stage the prothrombin time was 31 per cent of normal, but improved gradually after cessation of the bleeding. At the time of dismissal it had returned to normal. Platelet counts, bleeding and clotting times and clot retractions were normal. Serum proteins were normal, as were the A/G ratios.

Blood non-protein nitrogen and uric acid studies were normal. Repeated blood Eagle and Mazzini reactions were negative. All complement-fixation tests for gonor-

rhea were negative. Fieci and Ducrey skin tests were negative. Dark field examinations, smears and cultures of the penile excoriations failed to reveal any pathogens. No definite etiological agent was discovered in this case.

*Summary of Treatment* Many measures were tried. No response was noted after the administration of sulfonamides or penicillin. Vitamin K and calcium were given during the period of hematuria. Regardless of any therapy the patient continued to have symptoms. Bed rest is believed to be the only beneficial therapeutic measure in this case.

### INCIDENCE

There is no doubt in the minds of investigators that this syndrome occurs more frequently than reported in the literature. Almost all of the cases have been in young males, the majority having been in soldiers in the 20 to 30 year age groups. As far as we are able to determine there have been no cases reported in the negro race, however, when more work is done in this country there may be occurrences in this group also. The syndrome in an overwhelming majority is found in those without previous venereal history.

### SYMPTOMS AND CLINICAL FEATURES

The essential triad of symptoms has already been mentioned. However, there are other manifestations which should be cited. Lever and Crawford<sup>4</sup> reported cases of keratosis blennorrhagica without gonorrhea which were believed to be so-called Reiter's disease. Kuske<sup>5</sup> described nine cases of pseudo-gonorrheal dermatitis also having urethritis, conjunctivitis and arthritis. Kumer<sup>6</sup> discussed a rare feature of a pseudo-membranous and papulo-vesicular eruption not only involving the general skin, but also the mouth, nose, conjunctivae, prepuce and anus. Naegeli,<sup>7</sup> Wiedman,<sup>8</sup> and Kruspe<sup>9</sup> reported dermatological features in some of their cases.

Very rarely is there a septicemic course. A case was reviewed by Pfleger<sup>10</sup> which developed a peculiar type of septicemia accompanied by herpes of the cornea. Most of the cases develop a profuse purulent conjunctivitis and episcleritis with associated weeping and photophobia. Seldom does the temperature go above 38° C, but an occasional case has shown a fever of 39° to 40° C. Any complicating feature may give rise to a high febrile and marked toxic reaction. Night sweats are not uncommon.

Many have had their onset with a severe diarrhea, some even with a bloody flux, however, this symptom has not been constant enough to warrant its inclusion with the cardinal symptom-complex.

Excoriations and ulcerations of the penis have been present in a few cases. Most of the penile lesions occur as a result of the constant and profuse irritation from the urethral discharge. Pain in the perineum, suprapubic region, along the course of the urethra, and in the costovertebral regions may be present.

The joints are usually very painful, active motion is often impossible and passive motion produces excruciating pain. Polyarthritis is most frequently observed, but mono-articular involvement may occur.<sup>11</sup> There is often a marked synovial reaction which develops suddenly. One symptom may persist longer than others. Very few cases have suffered disabling features, however.

There are recurrences in about 20 per cent of the cases, with involvement of any or all of the three systems. The syndrome has a self-limited course—recovery usually being complete with little or no residue.

The prostate is frequently involved and has a tendency toward abscess formation. The seminal vesicles may become engorged and blocked, but there has been no instance of epididymitis reported.

### ETIOLOGY

The proof that Reiter's disease is an infectious process remains inconclusive, although evidence points to this probability. Very few investigators have recovered a definite bacteriologic agent. Reiter thought that a spirillum was responsible for this condition. Later studies showed that the causal agent is not a spirochete, since such an organism in succeeding cases has not been substantiated.

It has been observed by many workers that diarrhea often precedes or accompanies this syndrome. In the German armed forces an enteric polyarthritis frequently complicated by urethritis and conjunctivitis was extensively observed.<sup>12</sup> The factor of intestinal infection was considered. Many organisms have been cultured, most of them being non-pathogenic to animals. Gonococci have not been found in smears or cultures. The possibility that it is a venereal infection has been pretty definitely ruled out. No venereal history has been obtained in over 95 per cent of the cases and most cases have not had recent sexual exposure.

*E coli*, pneumococci, *Staphylococcus albus*, "enterococci" of various types, diphtheroids, non-hemolytic streptococci, *B. peritumescens* and *mucosus* are a few of the organisms found by investigators. Most of these organisms have not been recovered in animal studies. All cultures for tuberculosis have been negative.

Beigibock<sup>13</sup> suggests the possibility of allergy as being the etiologic factor. There is no information in the literature that this question has been studied or evaluated. We were able to rule this out as a basis in our cases.

Most investigators report sterile cultures when using ordinary bacteriological media. Because of the course and refractory nature of this syndrome, we expect to search for a filterable virus in the future with the hope of finding an etiologic agent.

### LABORATORY FINDINGS

In most cases the sedimentation rates are found to be increased, the rates rise and fall in relation to the acuteness of the attacks. Some may persist for a short time after the subsidence of the symptoms.

There is often a secondary hypochromic anemia, some cases revealing a red blood cell count near 3,500,000. The white cell count may be normal or elevated to 20,000. The average count hovers around 13,000 with the differential showing a slight increase in the polymorphonuclear elements.

The urine reveals many to clumps of pus cells, occasional to frequent red blood cells, traces of albumin, usually no casts, and normal concentration-dilution capacity.

The synovial fluids from the swollen joints fail to yield any causative agent. They show inflammatory cellular elements.

Serological tests for syphilis, complement-fixation for gonorrhea, and agglutinations for dysentery and Brucella have been negative. Non-protein nitrogen and uric acid studies are within normal limits. Thick and thin blood films have not revealed any foreign element or parasite in the blood stream.

Bauer and Engleman<sup>14</sup> give the best report on the pathological findings in the joints and synovial fluids. "The cytological and chemical alterations that occur in the synovial fluid are similar to the changes that have been observed in the specific arthritides. Biopsy of a joint during the acute phase reveals a markedly injected synovial membrane, which when examined microscopically shows intense hyperemia and small focal areas of acute inflammatory cellular infiltration, findings which are quite indistinct from the acute synovitis of either specific infection or rheumatoid arthritis."

Osteoporosis and atrophy of the bones may occur, especially in the subchondral areas. These are rare, however.

### DIAGNOSIS

A diagnosis of Reiter's syndrome is made by a process of elimination. The triad of urethritis, conjunctivitis and arthritis should make one suspect this particular entity after gonorrhea is ruled out by the negative history, smears, cultures, and complement-fixation tests. The presence of "sterile" cultures points to this symptom-complex. The course and the slow response to therapy make this condition more probable.

Because the arthritis may be the first and only symptom for a few days, it behooves us to differentiate this syndrome from the ordinary arthritides and rheumatic fever. Salicylates and chemotherapy apparently have no effect on Reiter's syndrome. The appearance of the urethritis and conjunctivitis will usually aid in differentiation.

### COMPLICATIONS

Rarely do complications occur. Cystitis and prostatitis are the most frequent. Balanitis has been reported in several cases. Colby<sup>15</sup> reports changes in the upper urinary tract in three cases. One developed a prostatic abscess which drained through the urethra. This case also had a terminal hematuria. No joint disability occurred. Another developed hydronephrosis with right chronic pyelonephritis. Cystoscopy showed a diffusely reddened bladder. The third patient showed hematuria with renal dilatation, which was improved at the time of discharge. One of Sommer's<sup>16</sup> cases developed a marked cystitis.

Many urinary tract complications respond to the element of time. Our cases have not been free of their symptoms long enough to perform any instrumentation, but during the previous episode, a cystoscopy showed a hemorrhagic cystitis. A secondary pyelitis may also occur.

Eye complications are infrequent. Episcleritis, iritis, and keratitis have been observed. The keratitis failed to cause permanent scarring. Herpes of the conjunctivae and cornea have also been recorded. Rarely permanent bone and joint changes take place.

### TREATMENT

Unfortunately, complete bed rest is the best treatment at our disposal at the present time. This has brought about slow but definite results. The average

case requires from six weeks' to three months' rest before the symptoms subside completely

A nutritious diet and adequate vitamin intake are essential since the weight loss must be corrected and the appetite stimulated

Beigibock<sup>17</sup> used "arthigon" in many of his 10 cases with surprisingly good results. This is a vaccine which produces a foreign protein reaction. Some of the patients had been treated before with other means but without benefit. An accidental observation while treating a suspected case of gonorrheal arthritis which later proved to be one of "Reiter's disease," induced Beigibock to use this vaccine in the other cases which now were definitely diagnosed as cases of Reiter's disease. Thus the preparation was used in all phases of the disease. The results were very encouraging. He concluded (1) the attacks of arthritis ceased after several injections, (2) there was freedom from pain at least for a few days, (3) there was a diminution in the stubborn effusions, (4) the conjunctivitis disappeared quickly, not to appear again, and (5) there was a diminution in the urethral discharge. This vaccine appears to be used quite extensively for this disease in Germany. Other workers have used sterile milk or other foreign proteins with encouraging results. We contemplated using typhoid vaccine or the hypertherm on our first patient, but his condition improved to such an extent that fever therapy was not thought advisable.

Codeine and sometimes morphine may be necessary to relieve the excruciating pain in the joints. Heat to the involved joints gives some relief. Salicylates have no appreciable effect. Sulfonamides and penicillin do not alter the course of the disease. Some German workers have used various urinary antiseptics but no definite improvement was seen. Antispasmodics are often helpful in relieving the pain in the lower urinary tract. Sometimes rendering the urine alkaline lessens the dysuria. The use of boric acid packs to the eyes followed by a bland antiseptic ophthalmic ointment will alleviate some of the eye symptoms.

Watchful expectancy for complications and giving them immediate attention will often avert future and permanent disability.

#### SUMMARY

We have endeavored to present two cases of the syndrome "Reiter's disease" in conjunction with a comprehensive review of the literature.

This syndrome is a definite clinical entity of unknown etiology, presumed to be infectious because of its clinical course. It is not due to gonorrhea and the possibility of its being a venereal disease is remote. The possibility that a virus is the etiologic factor is being investigated.

Complications are infrequent but may be very severe. The prognosis is usually good and recurrences are present in about one-fourth of the cases. There have been no cases cited in the literature which terminated fatally.

It must be assumed that the incidence is more frequent than appears from the literature. Since the syndrome is little known, many cases are not properly diagnosed or recognized.

In bringing the syndrome Reiter's disease to more general attention, especially to the clinician, bacteriologist, and pathologist it is our hope that further study will be given to this disease. Then the etiology could be ascertained and the therapeutic measures improved and evaluated.

## BIBLIOGRAPHY

- 1 REITER, HANS Über eine bisher unerkannte Spirochaetinfektion (Spirochaetosis arthritica), Deutsch med Wchnschr, 1916, xlii, 1535
- 2 BAUER, W, and ENGLEMAN, E P A syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's disease), Trans Assoc Am Phys, 1942, lvi, 307
- 3 ROPES, M W Personal communication to the author, 1944
- 4 LEVER, W F, and CRAWFORD, G M Keratosis blennorrhagica without gonorrhea (Reiter's disease?), Arch Dermat and Syph, 1944, ii, 389
- 5 KUSKE, HANS Über die Hauterscheinungen bei Morbus Reiter, Arch f Dermat u Syph, 1939, clxxix, 58
- 6 KUMER, H Diskussionsbekemerkung zur Reiterschen Erkrankung, Wien klin Wchnschr, 1934, xlvii, 1245
- 7 NAEGELI, H Reitersche Erkrankung, Sweiz med Wchnschr, 1938, lxxviii, 794
- 8 WIEDMAN, H Reitersche Erkrankung, Wien klin Wchnschr, 1934, xlvii, 1245
- 9 KRUSPE, S Zur Aetiologie der Reiterschen Erkrankung, Dermat Wchnschr, 1938, cxii, 457
- 10 PFLEGER, R Zur Aetiologie der Reiterschen Erkrankung, Med Klin, 1937, xxxiii, 465
- 11 BAUER, W, and ENGLEMAN, E P op cit, 312
- 12 BEIGIBOCK, W Über die Behandlungen der Reiterschen Erkrankung, Deutsch med Wchnschr, 1943, lxix, 803
- 13 IBID, 803
- 14 OP. CIT, 312
- 15 COLBY, F H Renal complications of Reiter's disease, Jr Urol, 1944, li, 415
- 16 SOMMER, A Drei wahrscheinlich als "Spirochaetosis arthritica" (Reiter) anzunehmende Krankheitsfälle, Deutsch med Wchnschr, 1918, xlv, 403
- 17 BEIGIBOCK, W op cit, 803

## EDITORIAL

### *MEDITERRANEAN ANEMIA*

THIS interesting disease was first clearly recognized as a distinct entity by Cooley,<sup>1</sup> who described the condition as it occurs in a severe form in children. Although the disease is relatively uncommon, Cooley's observations have been confirmed and amplified by many subsequent observers.

The disease is characterized by an increasing anemia which usually is not notable at birth, but becomes evident during infancy or early childhood and which progresses without remissions and in spite of treatment to a fatal termination within a few years or even a few months. In somewhat milder cases it may not be recognized until the tenth or fifteenth year and a few have survived into the twenties. There is progressive enlargement of the spleen and often of the liver, but no significant enlargement of the lymph nodes. The skin and sclerae are pale and yellowish, occasionally frankly jaundiced.

The blood shows a severe anemia which is microcytic and hypochromic in type, with usually a moderate reduction in the hemoglobin concentration. The red cell count is usually from 1,000,000 to 4,000,000 but is relatively higher than the hemoglobin or the volume of packed red cells. In blood films the red cells show highly characteristic changes. There is marked anisocytosis and poikilocytosis with a tendency to fragmentation of the cells and the development of bizarre distortions. The majority of the cells are small, although a few macrocytes are usually present, and they look thin and pale. There are usually (but not invariably) many "target cells,"<sup>2</sup> with a narrow rim and a circular central area of dark stained cytoplasm, often connected with the rim by a narrow "bridge," but elsewhere separated from it by a colorless zone. Such cells, however, may occur in a number of other diseases, including sickle-cell anemia.

In fresh wet films these abnormalities are even more conspicuous. Barrett<sup>2</sup> described bowl shaped cells with a thickened central area which he believed appear as "target cells" in stained films. There may be a tendency to ovalocytosis, but sickling has not been described.

Stained films show some diffusely polychromatophilic red cells, often many stippled cells, and usually many nucleated red cells which may be present in enormous numbers and justify the designation erythroblastic anemia. There are normoblasts and macroblasts but not typical megakaryoblasts. Reticulocytes are increased. There is often a leukocytosis, either lymphocytic or myeloid which may be high and accompanied by many myelocytes and myeloblasts.

<sup>1</sup> COOLEY, T. B., and LEE, P. Series of cases of splenomegaly in children with anemia and peculiar bone change, *Trans. Am. Pediatr. Soc.*, 1925, LVIII, 29-30.

<sup>2</sup> BARRETT, A. M. Special form of erythrocyte possessing increased resistance to hypotonic saline, *Jr. Path. and Bact.* 1938, XLVI, 603-618.



There is also an increased resistance of the red cells to hemolysis in hypotonic salt solution. Although the first trace of hemolysis may appear at about the same concentration as with normal control blood (0.46 to 0.44 per cent, but often much lower), most of the cells are undissolved in concentrations which hemolyze normal cells (0.4 to 0.3 per cent), and hemolysis may not be complete in 0.1 per cent salt solution, or even in distilled water. This resistance is due to the great thinness of the cells, which enables them to absorb a large volume of fluid before they reach a spherical shape and rupture. This is one of the cardinal features of the disease, although it may be observed, usually in less degree, in sickle cell anemia and other types of hypochromic anemia in which thin cells may be present.

There is usually some increase in serum bilirubin, and in the excretion of urobilin and urobilinogen, but evidences of hemolysis are usually mild. The fundamental abnormality appears to be a defect in blood formation, rather than accelerated destruction.

There is marked hyperplasia of the erythropoietic tissue, both extramedullary and in the bone marrow. This leads to peculiar characteristic changes particularly in the long bones and skull. The cortex is thinned and the medullary portion becomes widened and porous, so that in roentgenograms the trabeculae stand out like fine sharp spines, or "hair-on-end." The thickening of the bone may be so great that it gives the patient a mongoloid physiognomy, with high bulging forehead and prominent malar eminences. Similar changes, however, usually less marked, may occur also in severe cases of sickle cell anemia and familial hemolytic jaundice.

The cases reported have nearly all been in families of Italian and of eastern Mediterranean ancestry. Frequently two or more siblings are involved. In isolated instances, however, apparently authentic cases have been reported whose ancestry was Chinese, Negro, or Indian.

Interest in the disease was much increased by the observation of Wintrobe et al.<sup>3</sup> of a mild type of anemia in adults, which showed many of the cardinal features of Cooley's anemia of children. These observations have since been confirmed, notably by Dameshek<sup>4, 5</sup> and by Smith.<sup>6</sup> In most of these cases the anemia was slight and symptomless or virtually so. The red cell count was either moderately reduced or normal, occasionally somewhat increased. The cells, however, showed microcytosis and hypochromia, often in fairly marked degree. There were anisocytosis and poikilocytosis qualitatively similar to that in severe cases, which were usually well marked, and out of all proportion to the degree of anemia. Target cells

<sup>3</sup> WINTROBE, M. M., MATTHEWS, E., POLLACK, R., and DOBYNS, B. M. A familial hemopoietic disorder in Italians, *Jr Am Med Assoc*, 1940, cxi, 1530-1538.

<sup>4</sup> DAMESHEK, W. "Target cell" anemia: anerythroblastic type of Cooley's erythroblastic anemia, *Am Jr Med Sci*, 1940, cc, 445-454.

<sup>5</sup> DAMESHEK, W. Familial Mediterranean target-oval cell syndromes, *Am Jr Med Sci*, 1943, ccv, 643-660.

<sup>6</sup> SMITH, C. H. Familial blood studies in cases of Mediterranean (Cooley's) anemia, *Am Jr Dis Child*, 1943, lxxv, 681-701.

and oval cells were often present. The cells were thin, and they showed increased resistance to hemolysis in hypotonic salt solution. Films sometimes showed an occasional polychromatophilic or stippled red cell, but normoblasts were rarely found. Some splenomegaly, slight icterus and urobilinuria were occasionally present. In some cases an increase in nucleated red cells in the sternal marrow was demonstrated. Changes in the bones demonstrable in roentgenograms were usually trivial or absent.

The degree of the abnormalities noted in these cases varied greatly. In most of the cases they were moderate or slight. A few of the cases, however, showed gradations from this mild form to the severe type of Cooley.

One of the most interesting features of this group of mild cases is their familial occurrence, and their limitation to families of Italian and East Mediterranean origin. A study of apparently healthy members of the families of cases of outspoken Cooley's anemia has revealed that many of them show such minor abnormalities in the blood. In nearly all cases in which both parents could be adequately studied, abnormalities were found in both. The evidence is now convincing that these conditions are related, and that the disease depends upon an inherited constitutional defect.

The exact genetics involved in this inheritance has been a subject of study and speculation. Valentine and Neel<sup>7</sup> have recently reported an extensive study of four families, and have critically analyzed the published data bearing on the problem. The three theories which have been most seriously considered are (1) The outspoken form of the disease is inherited as a recessive character, and the patient is homozygous for this factor, i.e., inherits the defect from both parents.<sup>8,9</sup> (2) The disease (in either outspoken or mild form) is inherited as a dominant factor<sup>10</sup> for which the patient is heterozygous, and the varying degree of its expression depends presumably upon modifying genetic or environmental influences. (3) It is inherited as two nonallelomorphic dominant factors, one from each parent.<sup>10</sup> A statistical study of the number of normal individuals, mild and severe cases in these families revealed data which do not correspond perfectly with any theory, but conform best to the first theory of a recessive type of inheritance. The heterozygotes, carriers of the defect, however, show sufficient abnormalities ("mild cases") to make possible their recognition as a rule. If this theory is true, this offers an unusual opportunity to study the distribution of a recessive factor.

Although the "carriers" do not develop severe anemia, they are in varying degree abnormal individuals. Valentine and Neel suggested for them

<sup>7</sup> VALENTINE, W. N., and NEEL, J. V. Hematologic and genetic study of the transmission of thalassemia (Cooley's anemia, Mediterranean anemia), *Arch. Int. Med.*, 1944, **LXXIV**, 185-196.

<sup>8</sup> MONCRIEFF, A., and WHITBY, L. E. H. Cooley's anaemia, *Lancet*, 1941, ii, 648-649.

<sup>9</sup> COOLEY, T. B. Hereditary factors in the blood dyscrasias, *Am. Jr. Child Dis.*, 1941, **LXXI**, 1-8.

<sup>10</sup> MCINTOSH, R., and WOOD, C. L. An inquiry into the genetic factor in Cooley's anemia, *Am. Jr. Dis. Child*, 1942, **LXXI**, 192-193.

the term "thalassemia minor," as contrasted with the full-blown disease, "thalassemia major." They must be differentiated clinically from the iron deficiency anemias, lead poisoning, rheumatic fever, various forms of splenomegaly, as well as sickle cell anemia and various types of hepatic disease, in which target cells and increased resistance to hemolysis may be found

## REVIEWS

*The Chemistry and Physiology of the Hormones* Editor, FOREST RAY MOULTON  
Eighteen contributors 243 pages, 19 × 26 cm American Association for the  
Advancement of Science, Washington, D C 1944 Price, \$3.50 to members,  
\$4.00 to others

*The Chemistry and Physiology of the Hormones* is welcome at a time when there have been rapid advances in the field of hormones. It is made up of 17 papers which were originally presented in 1943 by outstanding investigators at the American Association for the Advancement of Science Gibson Island Research Conference. The original papers were revised in the light of the opinions expressed in the general discussion following their delivery and work appearing before the time of their final publication was included. The resulting compilation is an authoritative reference volume which should prove useful to the clinician as well as to the research worker.

Four papers are devoted to various aspects of the chemistry and the physiology of the pituitary hormones. The isolation, chemistry, and physiological activity of the adrenal hormones and of insulin are presented in four papers. Salter has reviewed the status of the hormonal iodine level of the blood in relation to thyroid function in a paper entitled "Euthyroidism and Thyroid Dysfunction." He points out the high degree of correlation between the clinical status of the patient and the hormone iodine levels of the blood but warns against the third use of the hormonal iodine level as an indicator of physiological status in all conditions.

The rapid advances made recently in the study of the adrenal and sex hormones have stimulated interest in some of their end products of metabolism. Two papers, "The Excretion of Steroid Hormones in Urine" and "Clinical Significance of Sex Hormones and 17-Ketosteroids," offer some interesting observations on the excretion of 17-ketosteroids by normal individuals and patients with various endocrinopathies. The qualitative and quantitative changes in the ketosteroid excretion in the diagnosis and in the prognosis of various endocrine disturbances are outlined. A paper by Schwenk presents some of the outstanding contributions to the synthesis of various steroids, presenting possible steps which might take place in the body. One needs a thorough knowledge of organic synthesis to follow some of these reactions. The application of any of these to *in vivo* synthesis is problematical as little is yet known about the synthesis of these substances in the body.

This series of papers serves to correlate many of the important findings in the hormone field and should prove a welcome addition to a scientific library. Over 1200 references are included in the bibliography.

M A A

## BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Pulmonary Edema and Inflammation* Harvard University Monograph in Medicine and Public Health—Number 7 By CECIL K. DRINKER M.D., D.Sc. 106 pages, 21.5 × 14.5 cm 1945 Harvard University Press, Cambridge Massachusetts Price, \$2.50

- Virus as Organism* Harvard University Monograph in Medicine and Public Health  
—Number 8 By FRANK MACFARLANE BURNET, M D, F R S 134 pages,  
21.5 × 14.5 cm 1945 Harvard University Press, Cambridge, Massachusetts  
Price, \$2.00
- A Primer of Electrocardiography* By GEORGE BURCH, M D, F A C P, and TRAVIS  
WINSOR, M D 215 pages, 24 × 15 cm 1945 Lea and Febiger, Philadelphia  
Price, \$3.50
- Government in Public Health* By HARRY S. MUSTARD, B S, M D, LL D 219  
pages, 21.5 × 14.5 cm 1945 The Commonwealth Fund, New York City  
Price, \$1.50
- Clinical Parasitology* By CHARLES FRANKLIN CRAIG, M D, M A (Hon ), F A C S,  
F A C P, Colonel, U S Army (Retired), D S M, and ERNEST CARROLL FAUST,  
M A, Ph D 871 pages, 24 × 15.5 cm 1945 Lea and Febiger, Philadelphia  
Price, \$10.00
- Fotografia Alergológica* By JOSE MARTORELLI 195 pages, 23 × 16 cm 1945  
El Ateneo, Buenos Aires, Argentina

## COLLEGE NEWS NOTES

### LIFE MEMBERSHIP

We are gratified to announce that Dr Merton M Minter, F A C P , San Antonio, Tex , is a recent addition to the Life Membership roster of the College

Many Fellows of the College who have been considering Life Membership would attain their ambitions and save money by completing their Life Memberships before the end of 1945 The Life Membership fee is deductible on Federal income tax returns Reports are rife that there will be at least moderate reductions in the income tax rate in 1946 The maximum saving from a tax standpoint, therefore may be made in completing Life Memberships in scientific organizations during the present year when the tax rate is at its highest level

The Life Membership fee in the American College of Physicians is worked out on an actuarial basis, varying in amount from \$100 00 for those 59 years of age or more to \$300 00 for those 45 years of age or younger Three hundred dollars is the maximum fee and from it \$15 00 is deducted for each year of age over 45, up to the age of 59, after which time \$100 00 is the minimum fee Life Membership entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions and to the official publications of the College, including Directories, Annals of Internal Medicine, etc Each Life Member receives a framed certificate, and his name is inscribed on the Life Member Scroll at the College Headquarters The College plan affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, thus avoiding the burden of dues later in life Quite aside from any personal advantages which Life Membership confers, members who can afford to do so should subscribe for the express purpose of putting the College in position, financially, to broaden its activities along lines which are clearly suggested at this time

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### ENLISTMENTS AND RETIREMENTS, A C P MFMBERS

The College has previously reported the names of 1,923 of its members who have been on active military service, and herewith reports the names of 4 additional members not previously included, bringing the total to 1,927

John E Gordon, Boston, Mass (Colonel MC, AUS)  
Seymour J Gray (Associate), Chicago, Ill (Lieutenant, MC, USNR)  
Hugh R Leavell, F A C P , Louisville Ky (Lieutenant Colonel USPHS, R)  
Walter C Nalty, F A C P . Fort Bayard, N M (Lieutenant Colonel MC, AUS)

The following members of the College have been honorably discharged

Ernest L Boylan Portland, Ore (Major, MC, AUS)  
Margil Clinton Carlisle, Waco, Tex (Captain, MC, AUS)  
Lee Pettit Gay St Louis, Mo (Major, MC, AUS)  
Edward A Hagmann Billings Mont (Major, MC, AUS)  
Andrew D Hart, Jr Charlottesville, Va (Lieutenant Colonel, MC AUS)  
Herman Albert Lawson, Providence, R I (Lieutenant Colonel, MC AUS)  
F A L Mathewson, Winnipeg Can (Group Captain, RCAF)  
Milton John Matzner, Brooklyn, N Y (Commander, MC USNR)  
Edgar M McPeak, San Antonio Tex (Major, MC AUS)  
Clark P Pritchett, Columbus, Ohio (Major, MC, AUS)

Edward G Thorp, Melrose, Mass (Lieutenant Colonel, MC, AUS)  
 Frank Walker Young, San Antonio, Tex (Colonel, MC, USA)

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications are gratefully acknowledged

#### *Reprints*

Robert M Craig (Associate), Chicago, Ill —1 reprint  
 Theodore R Failmezger, F A C P, Lt Col, (MC), AUS—1 reprint  
 Hyman I Goldstein (Associate), Camden, N J —1 reprint  
 Robert E Hobbs, F A C P, Major, (MC), AUS—1 reprint  
 Mack Lipkin, F A C P, New York, N Y —3 reprints  
 Edward W Miskall, F A C P, East Liverpool, Ohio—1 reprint  
 Carlisle Morse, F A C P, Louisville, Ky —1 reprint  
 Bernard M Scholdei, F A C P, Lieutenant Commander, (MC), USNR—1 reprint  
 George X Schwemlein (Associate), USPHS (R), Chicago, Ill —1 reprint  
 James S Sweeney, F A C P, Colonel, (MC), AUS—1 reprint  
 William G Talmage (Associate), Staunton, Va —1 reprint  
 Alexander S Wiener, F A C P, Brooklyn, N Y —12 reprints

Also acknowledged through non-member sources are the following

"The Role of Nutrition in Preventive Medicine," Mr A L Rose, Vice President, Mead Johnson & Company  
 A radio address, "Adequate Medical Care," American network, "The Doctors Talk It Over," by Dr David P Barr, F A C P, New York, presented to the Library on behalf of the Lederle Laboratories, one of the sponsors

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### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

#### *Pacific Medical Conference*

One of the most important medical meetings of this war was held in the Office of The Surgeon General of the Army, Washington, July 30-August 1, and was attended by outstanding experts in surgery, medicine and disease control from all theaters of operation throughout the world

Major General Norman T Kirk, The Surgeon General, called the meeting "to pool the knowledge and experience of the men from the fighting fronts in order that the lessons learned thus far in the war can be more thoroughly applied than ever before in the conservation of human life"

In addition to about forty of the country's leading medical experts from the overseas theaters, General Kirk had officers from virtually every division and branch of the Office of The Surgeon General attend the meetings and thoroughly discuss all phases of medical and surgical care, supply, transportation, training and related subjects

Such problems as the redeployment of millions of men to the Pacific areas were discussed. It was pointed out that the transfer of such vast numbers of American troops will invariably present health problems, but does not make the job impossible or unnecessarily difficult because of the experience of three and one-half years of facing and successfully fighting and controlling disease hazards of these areas

More effective means for the treatment and care of both wounded and sick,

troops near the front was another principal question studied at the meeting. It has been proved in the campaigns to date that such care has paid great dividends in the saving of lives and the alleviation of suffering, and the methods used are to be extended as far forward and as rapidly as is humanly possible.

Prevention and treatment of tropical disease were among the major problems studied and discussed at the meeting. Medical Corps specialists declared, however, that because many of these diseases are unknown in the United States, a dread of them has been created out of all proportion to their actual harmfulness.

The problem of returning medical personnel who have served several years in Pacific areas to the United States and replacing them with personnel from this country and the European and Mediterranean Theaters was given special study.

### *Major General George C. Dunham Cited for Inter-American Work*

Major General George C. Dunham, F A C P, United States Army, once referred to as the "World's Greatest Bug Hunter" in a citation by the American Hospital Association, was decorated with the Distinguished Service Medal at a ceremony in the Office of The Surgeon General on August 9, 1945.

Major General Norman T. Kirk, The Surgeon General of the Army, awarded the Medal to General Dunham on behalf of the War Department, and Nelson A. Rockefeller, Assistant Secretary of State and former Coordinator of Inter-American Affairs, read the citation in the presence of a large group of Army officials.

The citation stated in part that "for performing exceptionally meritorious service in a position of great responsibility from January 31, 1942, to June 8, 1945 in his capacity as Director of the Division of Health and Sanitation, Institute of Inter-American Affairs, Office of the Coordinator, and later as President of the Institute, General Dunham made a great contribution to inter-American relations."

General Dunham, detailed by the Army to the Office of Inter-American Affairs is well known as the "flying doctor of the Americas," since he directs more than 1,000 health centers, anti-malaria and other disease control projects, food supply, medical and nutritional surveys and experimental stations in conjunction with health authorities of the Republics concerned. These activities are carried on from Chile to the Central American Republics. They can be found deep in the Amazon regions of Brazil, Bolivia and Peru, and extend from the Caribbean Republics to the Atlantic.

About 12,000 persons are under the command of General Dunham at the many and varied activities scattered over the Americas and include doctors, nurses, dentists, sanitary engineers and other personnel. This work is carried on in four languages and many dialects. Many of his colleagues in the Republics refer to him as the doctor to 25,000,000 patients.

### *Madigan General Hospital Dedicated*

Dedication services were held at Madigan General Hospital, Tacoma, Washington, on August 20, 1945. On May 18, 1944, The Surgeon General reported that this installation, which was formerly Fort Lewis Hospital, be converted to a General Hospital for the Medical Department. This request was approved by the General Staff on May 26, 1944, and by the Federal Board of Hospitalization July 3, 1944. President Roosevelt signed the final papers on July 17, 1944.

Madigan General Hospital is named for Colonel Patrick S. Madigan (MC) F A C P. Colonel Madigan, after serving in France in World War I, remained in the Army, serving primarily as a neuropsychiatrist in this country and in the Philippines and Panama. At the time of his death, May 8, 1944, Colonel Madigan was stationed at Fort Belvoir, Virginia.



*Brigadier General Charles C Hillman, F A C P , Awarded Legion of Merit*

Brigadier General Charles C Hillman, (MC), U S Army, has been awarded the Legion of Merit for service from August 1939 to August 1944 "As Chief of the Professional Service, Office of The Surgeon General, by his untiring effort and devotion to duty he was responsible for the development of this Service from a small pre-war division to a large, well balanced organization Under his direction, physical standards were set up for the wartime Army, and professional direction was given to the blood plasma program and many other technical procedures which have been highly successful in the war effort "

*Yugoslav Award to General Leon Fox and Staff*

The Yugoslav "Medal for Services to the People" has been awarded to Brigadier General Leon Fox, F A C P , Field Director of the United States Typhus Commission, and to three other members of his staff

General Fox, a native of Birmingham, Alabama, was awarded the Order First Class, while the Order Second Class was given to Lt Col Edward Murray, Cedar Rapids, Iowa, Lt Col Charles Wheeler, Doon, Iowa, and to Naval Lt Stafford Wheeler, a graduate of Harvard Medical School, who was killed in Bosnia, April 13

Evidence of the Typhus Commission's services is shown by the fact that more than 2,000,000 persons have been immunized since the Commission came to liberated parts of Yugoslavia last January

*Promotions in the Army Medical Corps*

From Lieutenant Colonel to Colonel

Ralph Garnett Ball, F A C P , Manhattan, Kan

From Major to Lieutenant Colonel

Laurence Coleman Milstead, F A C P , Allentown, Pa

Hubert McKibban Parker, F A C P , Kansas City, Mo

William Ward Rucks, Jr , F A C P , Oklahoma City, Okla

*Surgeon General Announces New Officer Release Policy*

Under date of September 14, 1945, Major General Norman T Kirk, F A C P , The Surgeon General, announced a revised point system which will return 13,000 physicians, 25,000 nurses, 3,500 dentists and an undetermined number of other Medical Department officers to civilian life by January 1, 1946

Under the plan those Medical and Dental Corps officers who have 80 points, are 48 years of age or have been in the Army since before Pearl Harbor will be released as surplus officers unless they are specialists in eye, ear, nose and throat work, plastic surgery, orthopedic surgery, neuropsychiatry or are laboratory technicians These specialists will be released if they were called to active duty prior to January 1, 1941

This is a drastic lowering of points below the previous plan which was based on an adjusted service score of 100 for non-scarce Medical Corps officers and 120 for those in scarce categories

A similar drastic reduction was made in the point score for nurses, who are now eligible for discharge if their rating is 35 or more, or if they are 35 years old In addition, all married nurses and those with children under 14 years are eligible for immediate separation Physical Therapists and Dietitians are eligible under the same conditions if their point score is 40 or more, or if they are 40 years old

Veterinary Corps officers will be eligible for discharge if they have a point score of 80 or more, if they are 42 years old, or if they joined the Army prior to January 1, 1941

Medical Administrative and Sanitary Corps officers with point scores of 70 or more, who are 42 years of age or have been in service since before Pearl Harbor will be released as surplus

General Kirk added that in some cases essential officers may be retained by military necessity until replacements are shifted to their positions but none will be held in service after December 15, 1945, without their consent

Every effort will be made to release these officers at the earliest possible moment consistent with military needs, General Kirk added

It is also anticipated that, on the basis of an army of 2,500,000 men, a total of 10,000 doctors, 40,000 nurses and 10,000 dentists will be released by July 1946, and if the armies of occupation and troops in the United States are concentrated at large posts these figures will be exceeded. These figures represent approximately 70 per cent of the peak strengths at VE-Day of these corps

### *Dr Julian Ruffin Returns from ETO*

Dr Julian Ruffin, F A C P, Civilian Consultant to The Surgeon General, has just returned from ETO, where he replaced Dr Frederick Stare as clinician on Nutrition Survey Team No 1. During the time Dr Ruffin worked with this team, nutrition surveys were made in many cities in Germany

### *Typhus Award Made To Dr Francis G Blake and Dr Kenneth F Maxcy*

The United States of America Typhus Commission Medal was awarded by Major General Norman T Kirk, The Surgeon General of the Army, Monday, September 10 to Dr Francis G Blake, F A C P, Dean of Yale University School of Medicine, and Dr Kenneth F Maxcy, Professor of Epidemiology at Johns Hopkins School of Hygiene and Public Health, for "exceptionally meritorious service." Dr Blake's citation said in part "Dr Blake initiated and directed investigations of classical importance on the clinical features and prevention of scrub typhus. He made new contributions to the knowledge and control of a form of typhus fever of great military and civilian importance. His wisdom, energy and special competence assured the success of this mission and laid the basis for enduring benefits."

The Typhus Commission medal, which was authorized by the late President Roosevelt, is regarded as a high honor in this field of science. It has been awarded to date to only about 30 men.

### *Hospitals Named for Refresher Training Courses*

The Office of The Surgeon General has recently announced that the following hospitals have been designated for professional refresher training of Medical Corps officers to extend over 12-week periods:

Cushing General Hospital, Frammingham, Mass  
Mason General Hospital, Brentwood, Long Island, N Y  
Valley Forge General Hospital, Phoenixville Pa  
Kennedy General Hospital, Memphis, Tenn  
Newton D Baker General Hospital, Martinsburg, W Va  
Percy Jones General Hospital, Fort Custer, Mich  
Winter General Hospital, Topeka, Kan  
McCloskey General Hospital, Temple, Tex  
DeWitt General Hospital, Auburn Calif

Medical Corps officers desiring refresher training in neuropsychiatry will be permitted to serve the entire 12 weeks on the neuropsychiatric services and to rotate

through the various wards of the neuropsychiatric services in order to gain experience in all phases of neuropsychiatry

### *Dr William H Sebrell Completes Overseas Survey*

Dr William H Sebrell, F A C P, U S Public Health Service, acting as Nutrition Consultant to The Surgeon General, has recently returned from a 3-months tour of duty in ETO where he acted as Nutrition Consultant to Major General Stayer. Dr Sebrell directed the activities of the 5 nutrition survey teams operating in that area and proposed a permanent table of organization and equipment for such teams. At the request of General Stayer, he proposed an administrative organization for handling the data obtained, which proposal has in large part been accepted. Activities of the Medical Department and the food supply organizations were coordinated to the end that a more equitable food distribution in terms of need will result. Recommendations were made for improving transportation facilities for the distribution of food. This program, initiated in the Nutrition Division of The Surgeon General's office, is the first attempt yet made carefully to appraise the nutritional status of an entire nation and to control its food intake in terms of minimum physiological needs.

### *Enlistments of Doctors in Regular Army Sought*

Major General Norman T Kirk recently announced plans to interest Medical Corps officers who are serving for the duration of the war to apply for commissions in the Regular Army. Among the more important attractions which General Kirk listed are the following:

"1 The Regular Medical Corps officer will be assured a professional career offering broader possibilities in a larger field than the practice of the average civilian doctor affords.

"2 The training and the assignments of Army doctors will be arranged to aid the Army doctors in obtaining board certification for specialties from the recognized civilian specialty boards.

"3 Graduate training will be continued with the establishment of Army fellowships, residencies and special courses.

"In addition to the above attractions, which carry decided weight with any professional man, the Army affords security in its pension system, hospitalization care and other considerations not usually available in civilian practice."

The plans under this policy call for the establishment of graduate training programs at Army Installations where the residencies will meet the requirements of specialty boards and arrangements will be made for accrediting by the appropriate specialty boards. Another phase of the program includes the establishment of Army internships at selected Army general hospitals.

Plans outline a procedure for giving professional rehabilitation and specialized training to Regular Army Medical Corps officers who have been in administrative work during the war. These doctors who have not been able to engage in practice because of administrative responsibilities will serve as understudies with doctors who have been active in professional practice. This assignment will lead to continued professional service and eventually specialty board certification.

Medical Corps officers in the Regular Army will be kept in professional capacities without material interruption under this plan.

The advantages of a professional career in the Army will also be brought to the attention of medical students to interest them in an Army commission. Only those who stand scholastically in the upper third of their classes will be prevailed upon to consider the Army for a career.

Reserve or AUS officers now on active duty who desire consideration for commission in the Regular Army may forward through channels Statement of Interest to War Department Adjutant General's Office in accordance with the provisions of War Department Circular 243

Civilian physicians and former Organized Reserve Corps and AUS officers now on inactive duty status may submit Statement of Interest direct to the Adjutant General's Office

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As of October 1, Dr William B Dublin (Associate), previously of Los Angeles became pathologist at the Indianapolis City Hospital

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Dr Andrew D Hart, Jr, F A C P, who has been serving as Lieutenant Colonel in the Medical Corps of the Army, has been retired and is back as professor of clinical medicine at the University of Virginia, Charlottesville

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In recognition of his work on the various types of Rh factors and their genetic transmission, the College of Physicians of Philadelphia awarded, on July 14, 1945, the Alvarenga prize for this year to Dr Alexander S Wiener, F A C P, of Brooklyn Dr Wiener delivered the Alvarenga Lecture, "Rh Blood Factors in Clinical Medicine," before a combined meeting of the College of Physicians of Philadelphia and the Philadelphia County Medical Society on October 3

The Alvarenga prize was established by the will of Pedro Francisco daCosta Alvarenga, of Lisbon, Portugal, an Associate Fellow of the College of Physicians of Philadelphia, "to be awarded annually on the anniversary of the death of the testator, July 14, 1883" The award is made for outstanding published work and it is customary for the recipient to deliver his treatise before the College

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Lt Col Theodore L Badger, (MC), F A C P, has recently returned from thirty-nine months of service overseas in the European Theater of Operations He served there for two years as Chief of Medicine, Fifth General Hospital (Harvard Unit), subsequently being transferred as Consultant in Medicine and in Tuberculosis in England, France and Belgium During the last six months he was assigned as Medical Consultant of the Normandy Base Section

Col Badger is now separated from active duty with the Army and will renew the practice of medicine and diseases of the lungs at 264 Beacon Street, Boston

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Dr James L McCartney, F A C P, was released from active duty in the Navy on September 10, after forty months in uniform He just returned from fourteen months in the Pacific, where he was Chief of the Neuropsychiatric Department of a Naval Base Hospital in the Marianas Islands Commander McCartney was first commissioned in the U S N R in January, 1926 He is starting a clinic which will place special emphasis on the neuropsychiatric problems of returned officers and their families, and has opened offices in the Garden City Hotel, Garden City, Long Island, N Y

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The Department of Medicine Woman's Medical College of Pennsylvania, maintains an extensive library of films and slides, many of the films being 16 mm Kodachrome silent films Dr William G Leaman Jr, F A C P Director of the Department, has kindly made these films and slides available to the College or to visiting speakers, who might desire to use them Copies of the catalog and supplement of the films and slides can be obtained by writing or telephoning Miss Bruni, Department of Medicine, Woman's Medical College of Pennsylvania, Philadelphia 29, Pa

Dr Sarah I Morris, F A C P, who has been Professor of Preventive Medicine at the Woman's Medical College of Pennsylvania for several years, has resigned to accept an appointment as Resident Physician, and Professor of Hygiene at Wilson College, Chambersburg, Pa

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The Eighteenth Graduate Fortnight of the New York Academy of Medicine was held October 8-19, 1945. The subject this year was, "Contributions of the War Effort to Medicine." The program consisted of morning panel discussions, afternoon hospital clinics, evening addresses and scientific exhibits and demonstrations. Dr Cornelius P Rhoads, F A C P, is the Acting President of the Academy. Col William C Menninger, (MC), F A C P, delivered the Ludwig Kast Lecture on "Modern Concepts of War Neuroses." Dr David P Barr, President-Elect of the American College of Physicians and professor of medicine at Cornell University College of Medicine, gave a paper on "Physiological and Psychological Effects of Bed-rest," and Dr George W Thorn, F A C P, of Harvard Medical School, was a guest speaker on "The Use of Human Serum Albumin in the Treatment of Edema of Renal and Hepatic Origin."

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Every physician in the United States will receive during the coming months copies of a handsome new publication, "Your Doctor Speaks," issued by The Upjohn Company, leading manufacturers of pharmaceuticals. This book contains a series of health messages which have been appearing monthly in Hygeia, Parents Magazine, Life, Time, Newsweek and the Saturday Evening Post. The basic purpose of the book is to enhance the knowledge of the advances made by medical science and the doctor's ability to cope with disease, so that the public will seek medical attention whenever necessary and as soon as possible. The desire is to have the book placed in the physician's reception room where it will be available for patients to read.

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The Fifteenth Annual Conference of the Oklahoma Clinical Society has been scheduled for November 26-29, 1945, at the Biltmore Hotel, Oklahoma City.

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The Committee on Professional Education of the American Public Health Association announces it will undertake a program for the accreditation of schools of public health. The Association states the funds are made available through the generosity of the Commonwealth Fund and that Professor C-E A Winslow, of New Haven, has been appointed counsellor in charge of the investigative work. Accreditation will be based on a visit to the institution by a representative of the Committee and other data. A copy of the report of the staff will be submitted to the administrative head of the institution before submission to the Committee on Professional Education, and the Committee will provide a hearing to him or his representative if desired. Decisions of the Committee will be finally subject to approval by the Executive Board of the Association. In certain cases, provisional accreditation may be granted, subject to the fulfillment of specified requirements within a stated time.

It is planned to concentrate first on the basic one year of training qualifying for the degree of Master of Public Health (in Canada, Diploma of Public Health). At the same time, or subsequently, a list of institutions will be accredited for the more advanced degree of Doctor of Public Health, perhaps involving specialization in particular administrative or clinical fields.

Dr Stanton Tice Allison, F A C P, has been recently appointed to the rank of Captain, (MC), of the U S Naval Reserve. Capt Allison is Clinical Director and Chief of Medicine of the U S S Benevolence, one of the Navy's newest hospital ships, on duty with the Pacific Fleet

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Dr J C Geiger, F A C P, Director of Public Health of the City and County of San Francisco, recently received notice of his nomination as Honorary Vice-President of the Egyptian Public Health Association, notification being submitted through Dr A M Kamal, President of the Association

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Mr Basil O'Connor, President of the National Foundation for Infantile Paralysis, announces that the 1945 March of Dimes amounted to \$16,589,874, exceeding by more than fifty per cent 1944's unprecedented total

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The American Red Cross recently announced the appointment of Dr Louis I Dublin, assistant to the chairman of the American Red Cross and vice-president of the Metropolitan Life Insurance Company, to conduct a survey of child health in France, at the invitation of the French Government. Dr Dublin is accompanied by Dr Leona V Baumgartner, well-known pediatrician on leave to the Red Cross from the New York City Department of Health, and by Mrs Ida K Fivian, bi-lingual secretary, instructor in foreign languages at Bradford Junior College, Bradford, Mass. The Red Cross representatives will collaborate in their studies with French health agencies and with American Red Cross civilian war relief workers already in France. The survey, which is expected to be completed within two months, will seek ways in which assistance from abroad can help French health agencies to meet the needs of children

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The memberships of the following physicians in the American College of Physicians have been terminated

*Associates*

Max J Fein, New York, N Y  
Edward J West, Providence, R I

*Fellows*

Merle Q Howard, Wauwatosa, Wis  
William J McNerney, Syracuse, N Y  
William S Rude, Ridge Top, Tenn

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"Socialized Medicine" is the title of an interesting publication in Vol XXV, No 2, of The Index, published quarterly by The New York Trust Company. It is interesting to note that industrial and financial institutions are frequently interesting themselves in so-called "socialized medicine" and it is gratifying that they are supporting the viewpoint of the medical profession at large

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Dr J D Riley, F A C P, State Sanatorium, Ark has been elected President of the Arkansas Tuberculosis Association

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Dr William Earl Clark, F A C P, has been installed as of July 1, 1945, as President of the Medical Society of the District of Columbia. Dr Fred A J Geier, F A C P, was elected first Vice-President, and Dr William M Ballinger, F A C P, a member of the executive board

Dr Geier has been installed also as President of George Washington University Medical Society

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Dr Hugh R Leavell, F A C P., Louisville, Ky, for many years Director of the City-County Health Department, has resigned to accept a public health post with the Rockefeller Institute of Medical Research. He is now serving as a Lieutenant Colonel with the UNRRA, in London

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Capt Dar Delos Stofel, (MC), USNR, Kansas City, was recently awarded a commendation for meritorious and efficient performance of duty as executive officer of a fleet hospital in the South Pacific

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Dr Coy C Carpenter, F A C P., Winston-Salem, Dr Wilburt O Davidson, F A C P., Durham, Dr Walter R Berryhill, F A C P., Chapel Hill, Dr James W Vernon, F A C P., Morgantown, and Dr Paul F Whitaker, F A C P., Kinston, have been appointed to the Advisory Commission of the new North Carolina Hospital Board of Control

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Dr John W Preston, F A C P., Roanoke, Va, has been appointed to the Virginia State Board of Medical Examiners for a term of five years

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Dr Christopher C Shaw, F A C P., formerly of Bellows Falls, Vt, was advanced from Commander to Captain in the U S Naval Reserve on August 2, 1945. Captain Shaw is Chief of Medicine at the U S Naval Hospital, Corpus Christi, Tex

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Lt Col Theodore R Failmezger, (MC), AUS, F A C P., was Chief of Medicine and later Commanding Officer of the 116th Station Hospital in New Guinea and later in the Philippines. During his period as Commanding Officer, his hospital was awarded the Meritorious Service Unit Plaque

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Dr Thomas Addis, F A C P., Professor of Medicine, Stanford University School of Medicine, San Francisco, was made a Fellow of the Royal College of Physicians of Edinburgh on July 17, 1945

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Dr M A Shillington, F A C P., Glendive, has been elected President-Elect of the Montana State Medical Association

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Dr Nelson G Russell, Sr, F A C P., Buffalo, was recently honored at a special meeting of the city's advisory health board in recognition of his fiftieth anniversary of graduation from medical school

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Dr Arthur Grollman, F A C P., Professor of Experimental Medicine, Southwestern Medical College, Dallas, has been made Professor of Medicine and Chairman of the Department of Experimental Medicine

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Dr Eugene P Campbell, F A C P., has accepted an appointment as Chief of Field Party, Division of Health and Sanitation, the Institute of Inter-American Affairs, and is located in Rio de Janeiro, Brazil

Dr Beatrice Berle, wife of Ambassador Berle, has inaugurated a series of lectures on various clinical and public health problems, in which three members of Dr.

Campbell's staff have already participated. On August 15, with Dr Einor H Christopherson, Colonel Harold B Gotaas, Executive Vice President of the Institute of Inter-American Affairs, and a group of Brazilian public health physicians, Dr Campbell participated in the dedication of seven health centers in the Amazon Valley. These health centers have been constructed and are being operated through the Inter-American Cooperative Public Health Program under the direction of Major General George C Dunham, (MC), USA, F A C P

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#### KANSAS MEDICAL SOCIETY ESTABLISHES FUND TO ASSIST RETURNING VETERANS

The Kansas Medical Society will raise a fund of one hundred thousand dollars to assist returning Medical Officers in obtaining postgraduate medical education. Dr Harold H Jones, F A C P, Winfield, is Chairman. More than thirty-six thousand dollars is already available.

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Dr Hubert W Smith, formerly Research Associate at the Medical and Law Schools, Harvard University, has accepted an appointment as Professor of Legal Medicine at the University of Illinois Graduate School. Dr Smith graduated both in law and medicine, and has written many well known treatises on the subject of medicine and the law.

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Dr Harry J Perlberg, F A C P, Jersey City, has been elected President of the Radiological Society of New Jersey.

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#### CORRECTION

In the July issue of this Journal it was announced that Dr Theodore Rothman (Associate), formerly of Paterson, N J, had removed to Los Angeles where he had opened his office "for the practice of medicine." Dr Rothman specializes in neurology and psychiatry, and not in internal medicine.

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#### WAR-TIME GRADUATE MEDICAL MEETINGS

The sudden termination of active hostilities in both Europe and Japan, with the resultant anticipated redeployment and separation of physicians from service, has compelled the Central Committee to make preparations for the conclusion of the War-Time Graduate Medical Meetings. Unless more urgent demands are forthcoming, the activities will terminate as of December 31, 1945. The Regional Chairmen have already been communicated with.

#### *Partial Schedule of Future Meetings*

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey) Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

October 26—Recent Advance in the Treatment of Acute Intestinal Obstruction—Dr E L Eliason or Dr Robert Welty

November 16—Clinical Significance of Diplopia—Dr Walter I Lillie



REGION No 23 (Nevada, Northern California)—Dr S R Mettier, Chairman, Dr E H Falconer, Dr D N Richards

*Letterman General Hospital, San Francisco, California*

November 3—Uremia Following Urologic Surgery—Dr Donald Smith

*Station Hospital, Camp Stoneman, Pittsburg, California*

October 20—Suppurations of the Chest—Dr Clayton G Lyon

November 17—Plastic Surgery—Dr George Pierce

*Hammond General Hospital, Modesto, California*

October 21—Diagnosis and Surgical Treatment of Brain Tumors—Dr Edwin F Boldrey

November 21—The Use of Penicillin in Injuries and Infections—Dr Horace J McCorkle

*Station Hospital, Fort Ord, California*

October 27—Hemorrhagic States—Dr Paul M Aggeler

November 17—Diseases of the Thyroid Clinical Diagnosis and Management—Dr Mayo H Soley

*U S Naval Hospital, Mare Island, California*

October 26—Acute Sinusitis—Dr Lewis F Morrison

November 16—Streptococcal Infections—Dr Lowell Rantz

*ASF Regional Station Hospital, Oakland, California*

November 14—Diagnosis and Management of the Lymphomas—Dr Ernest F Falconer

*U S Naval Hospital, Treasure Island, California*

October 26—Peritoneal Injuries and Infections—Dr Alson R Kilgore

November 16—Interpretation and Misinterpretation of Certain Laboratory Tests—Dr James Hopper

*Station Hospital, Camp Roberts, California*

November 10—The Fundamentals of Endocrine Diagnosis—Dr Roberto F Escamill

REGION No 24 (Southern California)—Lt Comdr G C Griffith, Chairman, Dr V A Morrison, Capt H P Schenck, Dr J F Churchill, Maj N Nixon.

*Birmingham General Hospital, Van Nuys, California*

October 24—Communicable Diseases—Major Norman Nixon

Acute Infectious Mononucleosis—Captain Charles H Marple

November 14—Surgery of the Biliary Tract—Captain Howard K Gray

November 28—Thoracic Surgery—Captain W L Rogers

*ASF Regional Hospital, Camp Huan, California*

November 6—Hemolytic Streptococcal Diseases and Their Sequelae—Dr Robert Solley

*AAF Regional Station Hospital, March Field, California*

October 16—Tumor Pathology—Dr Edward Butt

November 20—Compound Fractures—Commander P E McMasters

*Station Hospital, Camp Cooke, California (afternoon session) and Hoff General Hospital, Santa Barbara, California (evening session)*

October 17—Traumatic Surgery of the Urinary Tract—Captain D W Atcheson

November 7—Some Dynamics of Military Neuro-psychiatry—Major Alexander Blumstein

November 21—Pericarditis—Lieutenant C Sylvester McGinn

*Toiney General Hospital, Palm Springs, California*

November 6—Psychosomatic Medicine—Major Milton Miller

Headache—Captain Oscar Sugar

November 20—Peptic Ulcer—Dr William Boeck

*U S Naval Hospital, Santa Margarita Ranch, Occanside, California*

October 25—Neurosurgery—Captain Everett Dickinson

November 8—The Cancer Problem in the Service Personnel—Lieutenant J S Binkley

November 22—Modern Concepts of Leprosy—Dr Maximilian Obermayer

*U S Naval Hospital, Long Beach, California*

October 17—The Streptococcal Problem—Lieutenant Commander George R Underwood

November 21—Liver Disease—Captain John Ruddock

*U S Naval Hospital, Corona, California*

October 25—False Biological Reactions—Major Mark Beam

Allergies—Major Iredell Hinnant

November 8—Neuropsychiatry—Lieutenant Commander Nichols

November 22—Tumor Pathology—Dr Edward Butt

*Station Hospital, U S Naval Air Training Station, San Diego, California*

October 19—Psychosomatic Medicine—Major Milton Miller

Headache—Captain Oscar Sugar

November 2—Recent Developments in Diabetes—Dr James Sherrill

November 16—Problems in Urology—Lieutenant Commander Rusche

*AAF Regional and Convalescent Hospital, Santa Ana Army Air Base, California*

October 18—Endocrinology—Dr Hans Lisser

November 6—Tuberculosis Problems—Commanders W L Rogers and A W Hobby

November 20—The Use of Products of Fibrinogen and Thrombin in Otolaryngology—Captain Harry P Schenck

*U S Naval Hospital, San Diego, California*

November 1—Dysenteries—The Differentiation Between the Protozoal and Bacillary Dysenteries—Dr John F Kessel

*U S Regional Hospital, Pasadena, California*

November 12—Thyroid Disease—Lieutenant Commander George Crile

## PUBLICATION OF MEMBERSHIP ROSTER POSTPONED

Early in the summer it was proposed to publish a revised Membership Roster of the American College of Physicians. To that end data were collected from members.

The end of the War in Europe and in the Pacific, with the subsequent shifting of Medical Officers and innumerable changes of addresses, makes it impractical to publish a complete Roster this year. Therefore, only a new and revised Supplement to the last Membership Roster (1943) will be published. This will be distributed to members in the late autumn.

It is hoped that the College can resume the publication of a complete Directory in 1946, for it is anticipated that the majority of its more than 1,900 members who are now on military service will have been retired to inactive status in the meantime.

*OBITUARIES*

## DR GEORGE H MEEKER

Dr George H Meeker, former Dean of the Graduate School of Medicine of the University of Pennsylvania, died September 4, 1945, at the age of 74.

Dr Meeker was born in Philipsburg, N J. He graduated from Lafayette College in 1893 and from the Medico-Chirurgical College of Philadelphia as a doctor of pharmacy in 1906 and thereafter completed a course in dentistry at the same institution. He did clinical research at the University of Munich, Germany. He had received honorary degrees from Ursinus College, Lafayette College, Villanova College and the University of Pennsylvania.

Although not a physician, he was Dean of the Medico-Chirurgical College until its merger with the University of Pennsylvania in 1916, from 1924 to 1928, he was also Director of the Graduate Hospital, and his Deanship of the Graduate School of Medicine extended from 1917 until 1941, when he retired. He was a member of the Masons, the Union League, Delta Upsilon, Phi Rho Sigma and Psi Omega fraternities, the American Pharmaceutical Association and the American Chemical Society. In 1906 he was the recipient of the Franklin Institute Medal for his contributions to science. A Clinic in Cincinnati, Ohio, was named in his honor.

Dr Meeker will be remembered by a great host of physicians who studied in the Graduate School of Medicine of the University of Pennsylvania, and who received advice and aid from him. Dr Meeker's unvarying objective was to establish in Philadelphia the finest and best school for postgraduate education in America.

## COLONEL CHARLES McCABE DOWNS

Colonel Charles McCabe Downs, of the regular Army Medical Corps, (Associate), has been reported killed in action on June 1, 1945. His candidacy for advancement to Fellowship would have been presented for action at the next meeting of the Credentials Committee and the Board of Regents.

Colonel Downs was born at Casey, Illinois, March 9, 1900. He held the degrees of B S and M D from Indiana University. He immediately entered the Medical Corps of the U S Army and interned at the Letterman General Hospital, San Francisco. His tour of duty preceding the war included the Letterman General Hospital in San Francisco and the Gorgas Hospital in Ancon, Panama, and his later assignments included Commanding Officer, 2nd Medical Squadron, 2nd Cavalry Division, October 1, 1941-July 15, 1942, Surgeon, 9th Armored Division, July 15, 1942-October 6, 1943, Commanding Officer, 110th Evacuation Hospital, Semmophile, Camp Swift, Texas, October 6, 1943-December 18, 1943, Surgeon, X Corps, December 18, 1943-. From July 5, 1944, he was serving in the Southwest

Pacific area, and on October 20, 1944, he landed in the Philippines, where he lost his life on June 1, 1945

Colonel Downs was a Fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He had a splendid record in the Army, and was considered well qualified in Gastroenterology and Pediatrics particularly

### EMANUEL KLAUS

Born May 4, 1875 of Joseph M and Hannah Klaus in Cleveland, "Manny," as he was affectionately known, attended Public School and matriculated in the School of Pharmacy, Western Reserve University. Graduated in 1892, at the age of 17, he practiced pharmacy for six years.

In 1898 he entered Western Reserve University Medical School and graduated in 1902. His immediate and lasting association was Lutheran Hospital on the West Side of Cleveland. He established his practice in its environs, eventually specializing in Internal Medicine. He was a pioneer in anesthesia.

While he was internist on the staff of Lutheran Hospital, he likewise held the office of Chief Anesthetist until 1937.

Owing to his interest in anesthesia he became associated with the late Dr F H McMechan and served as vice chairman of the Board of Governors of the Society of International Anesthesia Research from 1925 to 1939, at which time he succeeded Dr McMechan as Executive Secretary and held the post until his death.

Five years ago the Society awarded him a trophy "in appreciation of his devoted service to the world conquest of pain in behalf of a suffering humanity."

He was a member of The Temple and The Temple on the Heights. He rose to the 32nd degree of Masonry and was a member of the Shrine and Grotto.

He enjoyed the association of the A M A, American Board of Internal Medicine, Society of International Anesthesia Research and was a life member of the American College of Physicians.

Entering medicine in one war, the Spanish American, he served in the First World War as Captain in the Medical Corps at Camp Zachary Taylor, Kentucky and died during the Second World War on March 21, 1945. But he, peaceful, warm and kind, was the antithesis of war.

The world and particularly the West Side of Cleveland cannot help being better that "Manny" Klaus was born. It is a sad but true commentary on human nature that we are most conscious of the Good after it is gone. But the ideals which "Manny" begot in the minds of those who knew him are deathless forms. In living, "Manny" was a credit to man, to his Maker, to his race and to his art.

FRANK J DORAN, M D, F A C P,  
Cleveland, Ohio

## DR ABRAHAM RUDY

Abraham Rudy, M D , F A C P , Boston, Mass , died February 19, 1945, of pulmonary neoplasm, aged 50 Dr Rudy was born in Bialystok, Poland, February 20, 1895 He was naturalized in the United States of America in 1928 His training was received in his native land of Poland, at the Academie de Caen, Rouen, France, and XI Gymnasium, Moscow He graduated in medicine in 1923, Friedrich Wilhelm's University of Berlin In this country he did postgraduate work at the Psychiatric Institute, Morristown, N J , New York Post-Graduate Medical School, and Harvard Medical School

Dr Rudy had been on the faculty of Tufts College Medical School since 1929 He was Associate Visiting Physician, Chief of the Diabetic Clinic, and Consultant in Diabetes, Beth Israel Hospital, Visiting Physician and Consultant in Diabetes, Jewish Memorial Hospital, and Consultant in Diabetes, Jewish Tuberculosis Sanatorium, Rutland Dr Rudy was a member of many medical organizations, and had been a Fellow of the American College of Physicians since 1942 He was the author of numerous published articles and of "Simplified Diabetic Manual" and "Practical Handbook for Diabetic Patients"

## DR FRANK NEAL

Frank Neal, M B , M R C S (England), L R C P (London), F R C P (Canada), F A C P , Peterborough, Ontario, Canada, died suddenly of a heart attack on January 18, 1945 His death has not previously been recorded in these columns

Dr Neal was born at Brussels, Ontario, September 3, 1879 He received his degree of Bachelor of Medicine in 1903 from the University of Toronto Faculty of Medicine He later did postgraduate work, in London, England, and became a member of the Royal College of Surgeons of England and a licentiate of the Royal College of Physicians of London For many years he was connected with the Nicholls Hospital and St Joseph's General Hospital of Peterborough He was Consultant in Internal Medicine at St Joseph's General Hospital, Director of the Diagnostic Chest Clinic of the Peterborough Health Association, Director of the X-Ray Department, and Consultant in Chest Diseases at the Nicholls Hospital, and Director of the Standard Medical and Surgical Clinic

Dr Neal had been President of the Ontario Medical Association, 1933-34, a Counsellor of the Canadian Medical Association, 1933-35; Chairman of the Ontario Laennec Society, 1934-35 and Vice-President of the American Therapeutic Society, 1934-35 He had also been President of the Ontario Radiological Society, and was a member of the Radiological Society of North America Dr Neal became a Fellow of the American College of Physicians in 1923 Like many other medical men in these times

he had been working much too hard for some years, and at the end of a particularly heavy day, while examining his last patient about 6 30 in the evening, he collapsed and died before help could reach him

### DR DONALD RENWICK FERGUSON

The many friends and former students of Major Donald Renwick Ferguson of Philadelphia, Pennsylvania, were shocked to hear of his sudden death from a cerebral hemorrhage at Camp Shanks, New York, on Monday, August 27, 1945

Major Ferguson was born at Ben Avon, Pa., November 21, 1889. After graduating from the Central High School in Philadelphia, he attended Swarthmore College and received the degree of A B in 1912. He then pursued his medical studies at the Hahnemann Medical College and graduated in 1916. He served as Chief Resident at Hahnemann Hospital, 1916-1917, and served in the First World War as Captain in the Medical Corps from 1917 to 1919. On the termination of the First World War he returned to Philadelphia and became associated with the teaching corps of the Hahnemann Medical College of Philadelphia, serving as Associate Professor of Medicine and later as Clinical Professor of Medicine. In 1938 he was made visiting physician to the Hahnemann Hospital of Philadelphia. He also served as visiting physician and cardiologist at St. Luke's and Children's Hospital and consulting cardiologist at the Women's Homeopathic Hospital.

Major Ferguson took an active interest in various medical organizations and served as President of the Homeopathic Medical Society of the County of Philadelphia. He was also a member of the Board of Control of the American Institute of Homeopathy, Secretary of the Homeopathic Medical Society of the State of Pennsylvania and was a member of the Oxford Medical Club, Philadelphia County Medical Society, Medical Society of the State of Pennsylvania and the American Medical Association.

He became an Associate of the American College of Physicians in 1923 and a Fellow in 1928. At the break of the Second World War, Dr. Ferguson volunteered his services in the Medical Corps and served as a Major from September 25, 1942, until the time of his death.

Dr. Ferguson will always be remembered by those with whom he was associated as an exponent of the highest ethical standards in medical practice and as a forceful and enthusiastic teacher in his chosen field of clinical medicine. His loss will be deeply felt by his many friends and by the institutions that he served so faithfully and so long.

G HARLAN WELLS, M D, F A C P,  
Philadelphia

## DR WILLIAM S STREKER

Dr William S Streker, F A C P, died suddenly at his summer home at Hyannis, Massachusetts, on July 8, 1945. He had previously shown evidence of arteriosclerotic heart disease.

Dr Streker was born in Providence on October 11, 1885. He attended public schools in Providence and was graduated in 1908 at the Jefferson Medical College of Philadelphia. He took postgraduate work in internal medicine at the Harvard Medical School and at the Peter Bent Brigham and Massachusetts General Hospitals. In 1931 he became a Fellow of the College. At the time of his death he was Physician-in-Chief at the St. Joseph's Hospital and Consultant at the State Sanatorium at Wallum Lake. He was a diplomate of the American Board of Internal Medicine.

Dr Streker was President of the Providence Medical Association in 1936. In this capacity he served the community particularly well as he initiated certain changes in the organization which have been of lasting benefit.

He is survived by his wife and four brothers, two of whom are physicians and one a dentist, as well as by three sisters, two of whom are graduate nurses. Throughout his professional career he proved himself to his many patients always a kindly, tactful physician and a faithful friend.

ALEX M BURGESS, M D, F A C P,

Governor for Rhode Island

## DR JOHN C GRILL

John C Grill, M D, F A C P, Milwaukee, Wisconsin, died of a cerebral hemorrhage on March 17, 1945, at the age of 52. His death has not previously been recorded in this journal. Dr Grill was born in Vienna, Austria, August 25, 1892. He attended the State Gymnasium at Vienna and received his medical degree from the University of Vienna. He had been Professor and Director of the Department of Pathology at Marquette University School of Medicine, Milwaukee, for several years. He was Director of Laboratories at the Milwaukee County Hospital and Pathologist at St. Mary's and St. Joseph's Hospitals, Milwaukee.

Dr Grill was a member of the Milwaukee County Medical Society, Wisconsin State Medical Society, American Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists, and the Central Society for Clinical Research. He was a Fellow of the American Medical Association and a former President of the Milwaukee Pathological Society. He was a Diplomate of the American Board of Pathology, and had been a Fellow of the American College of Physicians since 1938.

## DR WILLIAM WALLACE HALL

William Wallace Hall, M D, F A C P, Watertown, New York, died January 3, 1945, but his death has not previously been recorded in these



columns Dr Hall was born at Addison, Steuben County, New York, January 26, 1887. He received his B S degree in 1913 and his M D degree in 1917 from Syracuse University. He had done postgraduate work at Harvard Medical School, and at the time of his death was Chief of the Medical Service, House of the Good Samaritan, Watertown. Dr Hall was a member and past President of the Jefferson County Medical Society, a member of the New York State Medical Society, and American Diabetes Association, a Fellow of the American Medical Association, and a Fellow, since 1931, of the American College of Physicians.

### DR HENRY IRWIN KLOPP

Henry Irwin Klopp, M D , D Sc , F A C P , Allentown, Pa , died March 7, 1945, but his passing has not previously been recorded in this journal. Dr Klopp was born at Stouchsburg, Berks County, Pa , in 1870. He attended Albright College, and graduated in medicine from Hahnemann-Medical College of Philadelphia in 1894. He interned at the Reading Homeopathic Hospital.

Early in his career Dr Klopp entered upon the specialty of psychiatry and served successively as Assistant Physician, Assistant Superintendent, and Acting Superintendent of the Westboro (Mass ) State Hospital. He was Superintendent and Physician-in-Chief of the Allentown State Hospital. He was Professor of Mental Diseases, Department of Neurology and Psychiatry, Hahnemann Medical College and Hospital of Philadelphia. Dr Klopp was a Diplomate of the American Board of Psychiatry and Neurology, a member of the Lehigh County Medical Society, Lehigh Valley Homeopathic Medical Society, Philadelphia Psychiatric Association, Pennsylvania State Homeopathic Medical Society, Association of Medical Superintendents for Mental Disease, and American Psychiatric Association, in 1940-41 he was President of the Pennsylvania Psychiatric Society. He had been a Fellow of the American College of Physicians since 1923, and more recently became a Life Member.

### DR FERGUS OLAMH MAHONY

Fergus Olamh Mahony, M D , F A C P , El Dorado, Arkansas, died February 6, 1945, aged 65 years. He was born in El Dorado, July 30, 1879, attended the University of Arkansas, and received his medical degree in 1908 from Tulane University of Louisiana School of Medicine. He returned to his alma mater frequently in succeeding years for postgraduate study. He was for many years Surgeon, Missouri Pacific Railroad. From 1921 to 1927 he was El Dorado City Health Officer, and from 1920 to 1929, Union County Health Officer. He had for many years been Chief of Staff, Warner-Brown Hospital. He was a former President of the Arkansas State Board of Health. Dr Mahony had been honored with the Presidency

of the Arkansas State Medical Society and the Union County Medical Society. He was a member of the Southern Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1930.

### DR THOMAS WILLETT

Dr Thomas Willett (Associate), West Allis, Wisconsin, died of myocardial fibrosis, February 25, 1945. He was born in 1877 and graduated in 1903 from the Wisconsin College of Physicians and Surgeons. He had been formerly associated with the Public Health Service Reserve and served overseas during World War I as Lieutenant Colonel, Medical Reserve Corps, U S Army. At one time Dr Willett was Medical Director of the Milwaukee County Hospital for Tuberculosis, and Clinical Director of the Milwaukee South Side Children's Clinics. He was Director of the Milwaukee County Bank at West Allis.

Dr Willett was a member of the County and State Medical Societies and the Milwaukee Academy of Medicine. He was a Fellow of the American Medical Association, and had been an Associate of the American College of Physicians since 1927, having become an Associate before it became compulsory to qualify for advancement to Fellowship in any particular period. It is regretted that an earlier obituary could not be obtained for record in these columns.

### DR BERNARD ISAAC COMROE

Bernard Isaac Comroe, M D , F A C P , died suddenly at his home in Philadelphia on September 14, 1945, at the age of 38. Born in York, Pa , in 1906, he entered the University of Pennsylvania at the age of 15 and graduated from its Medical School in 1929. His undergraduate career was one of distinction and brilliance. The promise shown there was abundantly fulfilled in his subsequent short life. He filled an important place in the faculty of his alma mater and was known widely as a student of his chosen specialty arthritis. Among his numerous publications were two well known textbooks "Internal Medicine and Dental Practice" and "Arthritis and Allied Conditions". He will be long thanked by the graduates of the University of Pennsylvania who served in the Armed Forces for a little bulletin of Philadelphia news which he prepared and sent them. He was a member of a number of societies and organizations. These included Fellowship since 1937 in the American College of Physicians.

The American College of Physicians has sustained a real loss in the death of this very able and promising young physician. Our sympathy goes to all of his family but particularly to his father, Dr Julius Comroe, Sr , of York, Pa , who is also a Fellow of the American College of Physicians.

THOMAS M. McMILLAN, M D , F A C P ,  
Governor for Eastern Pennsylvania

## DR ALEXANDER HAMILTON STEWART

Alexander Hamilton Stewart, M D , F A C P , Harrisburg, Pa , died on July 31, 1945 Dr Stewart was born in Plumville, Indiana Co , Pa , on July 22, 1880, and was graduated from the University of Pittsburgh School of Medicine in 1907 After his internship in the Columbia Hospital, Wilkensburg, Pa , and postgraduate work at Harvard University and the Cleveland Clinic, he returned to his home, where for many years he was a member of the medical staff of the Indiana Hospital and Medical Director of Indiana County He was Secretary and later President of the Indiana County Medical Society In the Pennsylvania State Medical Society, Dr Stewart held important and responsible positions, having been Chairman of the Public Health Legislation Committee and formerly a member of the Board of Trustees Dr Stewart had been a Fellow of the American College of Physicians since 1926 Dr Stewart is best known through his work in the Pennsylvania State Department of Health, in which he served a number of years In 1939 he was made Deputy Secretary of Health Later he was appointed Secretary of Health and held the latter important position at the time of his untimely death

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## AZOTEMIA IN TYPHUS FEVER<sup>1</sup>

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THE factors which may be responsible for the development of azotemia in severe infectious diseases have been recently reviewed<sup>1</sup>. The diagnosis of azotemia depends upon the biochemical analysis of the patient's blood in a well-equipped laboratory. In typhus fever it is to be expected that under the extremely adverse conditions of hospitalization which are frequently found during epidemics of this disease, azotemia may be unrecognized in many patients. It is, therefore, understandable why comparatively little information on the subject of azotemia is found in the general literature on typhus.

Woodward and Bland in a recent paper<sup>2</sup> called attention to the presence of azotemia in severely ill typhus cases. Azotemia was said to have been universally present in comatose patients. The authors believed that dehydration accounted for azotemia in many of the cases, and stated that adequate fluid replacement often overcame this condition. The presence of other factors such as protein destruction, reduced glomerular filtration resulting from an "unstable circulation," and hepatic dysfunction were believed to account for the development of nitrogen retention in certain cases. Other general descriptions of clinical typhus fever in the English literature which we have been able to review seldom mention the presence of azotemia or its significance<sup>3, 4, 5, 6, 7, 8</sup>.

In 1862 Murchison noted an increase in the blood urea nitrogen in typhus fever<sup>9</sup>. In 1920 Wagner found an elevation of the blood non-protein nitrogen above 100 mg per 100 cc in 15 of 76 typhus cases studied<sup>10</sup>. More recent reports in the German and French literature have discussed the cause of azotemia in typhus<sup>11, 12, 13, 14, 17</sup>.

\* Received for publication July 9, 1945

From the Cairo Unit of the United States of America Typhus Commission

There has been no general agreement as to what factors may enter into the genesis of azotemia in typhus. The presence of glomerular nephritis at autopsy has been found as high as 68 per cent in one large series of cases<sup>16</sup> and very rarely in others<sup>5, 10</sup>. Reports on fatal cases with uremia have stated that glomerular nephritis was either absent<sup>14</sup> or minimal<sup>17</sup>. In a recent review article on uremia in typhus it is stated that a "serosal" type of nephritis, the "inflammatory edema of the kidney" of Fahr, may result in nitrogen retention<sup>14</sup>. It has also been said that an "hepato-renal syndrome" may occur, with nitrogen retention and jaundice<sup>28</sup>. The association of hypochloremia and azotemia has been found by some investigators<sup>17</sup> and not by others<sup>12, 14</sup>. Aschenbrenner<sup>14</sup> has recently remarked that uremia in typhus appears to be the result of an increase in protein destruction with a reduction in the excretory ability of the kidneys, brought about by inflammatory or functional changes. However, the author calls attention to the fact that in typhus the diagnosis of glomerular nephritis is extremely difficult to substantiate, and states that only observation over a considerable period of time can confirm the diagnosis. In fatal cases he observes that the microscopic findings in the kidneys are quite variable.

There have been numerous clinical reports on large series of typhus cases studied by German investigators in the past three years, concerning cardiovascular disturbances,<sup>15, 18, 19</sup> the effect of convalescent serum and whole blood,<sup>20, 21, 22</sup> the effect of typhus vaccine on the course of the disease,<sup>23, 24</sup> as well as general clinical discussions of typhus<sup>25, 26, 27</sup>. There are no comments in these papers concerning the presence and incidence of azotemia in typhus, its relation to the severity of the disease, or to the fatality.

It is our belief that the establishment of the presence or absence of azotemia is of interest to the clinician in charge of typhus patients. Its presence not only poses many interesting questions concerning the pathologic physiology of typhus, but, when considered with the clinical picture as a whole, it has been in our experience of considerable aid in indicating desirable measures for supportive treatment. The purpose of this paper is to emphasize the frequency with which nitrogen retention occurs in epidemic typhus, to point out its relation to the severity of the clinical course of the disease, and by the presentation of typical cases of severe or fatal typhus to call attention to certain factors which appear to be of significance in the development of this condition.

*The Background for Reported Observations* In the two seasons, 1943 and 1944, 159 cases of typhus fever were admitted to the United States of America Typhus Commission ward at the Cairo Fever Hospital<sup>29</sup>. It was possible also to observe numerous cases of typhus fever on the general typhus wards of the hospital. With the exception of three patients, all of the typhus cases studied on the Commission ward were Egyptian males, their ages ranging from 10 to 70 years. By far the greater number of patients were in the 21-35 year age group. These cases were selected either from the

general typhus wards of the hospital or from the receiving ward. In general the attempt was made to study patients as early in the disease as possible. The majority of cases were admitted between the fifth and tenth day of their illness. We were fortunate to obtain a few cases in the first day of the clinical disease, and in four instances to observe patients before the onset of their disease. A comprehensive picture of louse-borne typhus fever, as it occurs in epidemic form, was obtained.

The patients observed on the Commission ward and on the general wards of the Fever Hospital were considered to be suffering from epidemic louse-borne typhus fever. In many instances it was possible to recover rickettsiae from the blood of the patients or from normal lice fed on patients. Every strain thus far isolated has shown the characteristics of louse-borne typhus<sup>30,32</sup>. In addition, the clinical diagnosis of typhus fever was supported in nearly every instance by the Weil-Felix agglutination reaction or complement fixation tests<sup>31,32</sup>. Postmortem examination was made in nearly all of the cases which died on the Commission ward. The results of these post-mortem examinations will be reported at a later date.

Many patients admitted to the Commission ward were given various therapeutic agents specifically directed against the disease<sup>33,34</sup>. A few patients, hospital employees, contracted typhus after vaccination and were studied in the Commission ward. The data from these patients are described elsewhere<sup>35</sup>.

The present paper is restricted entirely to the consideration of the unvaccinated patients who received no special therapy except supportive measures. There were 64 such cases studied on the Commission ward from whom data are available for inclusion in this report. It was possible to obtain additional information on many of these patients on follow-up visits to the Commission ward. These 64 cases are termed "untreated" cases of typhus fever. In addition, data were obtained on 14 patients observed on the general typhus wards of the hospital, who are referred to in this paper as "Cordon" patients.

Early in the course of our observations on typhus fever in Egypt it became apparent that the most severely ill cases showed abnormal concentrations of the blood non-protein nitrogen. In some patients nitrogen retention\* was accompanied by symptoms and signs suggestive of uremia. Factors contributing to the development of azotemia, such as a pronounced hypotension, or severe dehydration, were clearly evident in some cases. A few cases observed in the Commission ward appeared to develop azotemia in the absence of the obvious contributing factors mentioned above. The constancy with which nitrogen retention was present or developed in fatal cases who came under observation in the past two seasons has indicated the high incidence of this condition associated with death from typhus fever.

\* Blood non-protein nitrogen values of 45 mg per 100 c.c. or higher are interpreted as evidence of nitrogen retention, or azotemia.

*Presentation of Data* In these studies the concentrations of the blood urea nitrogen and creatinine were determined as well as the concentration of the non-protein nitrogen in many instances. In practically all cases the trend of concentration of the blood urea nitrogen and creatinine was similar to that shown by the non-protein nitrogen. For the sake of simplicity, therefore, the concentration of the blood non-protein nitrogen is discussed throughout this paper.

*Estimation of Severity of Illness* After discharge from the Commission ward, the severity of the clinical course of the disease was estimated for each patient. The factors which influenced the estimation of severity, and the classification of illness have been described elsewhere<sup>34</sup>. In brief, each patient was classified in one of the following groups:

"B" Cases with minimal symptoms and signs of typhus

"C" Cases of moderate severity

"D" Severely ill cases

"E" Severely ill cases in which fatal outcome was expected at some point in the disease

"F" Fatal cases

*The Incidence of Nitrogen Retention and Death in Typhus Fever* Fifteen of the 64 patients in this study died during the course of the disease, a mortality of 23 per cent (table 1). Thirty-three of the cases (52 per cent) developed nitrogen retention during the disease. The 15 fatal cases were in this group. No deaths occurred in the group of patients who had normal blood non-protein nitrogen concentrations throughout their illness.

TABLE I

The Incidence of Fatal Cases among the Patients \* Who Had Normal Blood Non-Protein Nitrogen Concentrations and the Patients Who Had Nitrogen Retention †

| Year   | Number of Cases | Cases without Nitrogen Retention |        | Cases with Nitrogen Retention |        |
|--------|-----------------|----------------------------------|--------|-------------------------------|--------|
|        |                 | Number                           | Deaths | Number                        | Deaths |
| 1943   | 29              | 14                               | 0      | 15                            | 7      |
| 1944   | 35              | 17                               | 0      | 18                            | 8      |
| Totals | 64              | 31                               | 0      | 33                            | 15     |

\* Unvaccinated "untreated" Egyptian males between 10 and 70 years of age observed on the Commission ward at the Cairo Fever Hospital.

† Values for the blood non-protein nitrogen of 45 mg per 100 c.c. or higher are regarded as evidence of nitrogen retention.

*The Relation of Nitrogen Retention to the Age of the Patient* The average age of the 64 patients in this study was 28 years. The average age of the 15 patients who died was 33 years. There were 18 patients in the group of 33 with nitrogen retention who recovered. The average age of these patients was the same as that of the patients with no nitrogen retention (table 2). It is to be noted, therefore, that nitrogen retention was not restricted to the older age group of typhus fever patients.

*The Time of Onset of Nitrogen Retention in Typhus Fever* In our experience nitrogen retention developed most frequently in the second week of typhus fever. For example, six fatal cases, admitted on the fourth, fifth, and sixth days of illness, had normal blood non-protein nitrogen concentrations on admission and first began to show elevated values between the ninth and eleventh days of illness.

TABLE II

The Incidence of Nitrogen Retention and Death in Relation to Age in Typhus Fever \*

|                 | Cases with No Nitrogen Retention | Cases with Nitrogen Retention |      | Total |
|-----------------|----------------------------------|-------------------------------|------|-------|
|                 |                                  | Recovered                     | Died |       |
| Number of cases | 31                               | 18                            | 15   | 64    |
| Average age     | 27                               | 27                            | 33   | 28    |

\* Footnotes as in table 1

In a few instances, however, nitrogen retention was encountered in the first week of illness. Three cases in the group of 30 who were admitted before the eighth day had elevated blood non-protein nitrogen concentrations on admission, one was a "D" case, and two were "E" cases. One fatal case whose blood was first examined on the eighth day of illness had a non-protein nitrogen concentration of 96 mg per 100 c c. It was very probable that this patient had nitrogen retention before the seventh day of illness.

*Nitrogen Retention and the Severity of Illness* In 14 cases of moderate severity ("C" 's), four showed nitrogen retention at the time of hospital admission (table 3). These four cases entered the ward in the second week

TABLE III

Comparison of Nitrogen Retention and Severity of Illness \* in 64 Cases of Typhus Fever †

| Classification of Severity | Total Number of Cases in Each Classification | Cases with Nitrogen Retention |  |
|----------------------------|--|-------------------------------|--|
|                            |  | Number in Each Classification | Per Cent of Total in Each Classification |
| "B"                        | 2  | 0                             | 0  |
| "C"                        | 14   | 4                             | 29                                       |
| "D"                        | 26   | 9                             | 35                                       |
| "E"                        | 7  | 5                             | 72                                       |
| "F"                        | 15   | 15                            | 100                                      |

\* The criteria for classification of severity appear in the text

† Footnotes as in table 1

of illness. Their blood non-protein nitrogen concentrations fell to normal soon after admission. There was no evidence of oliguria or marked hypotension in these patients.

The severe cases of typhus showed azotemia in greater proportion. Five of the 14 cases with azotemia in groups "D" and "E" developed this condi-



tion while under observation The others had azotemia at the time of admission

As may be seen from tables 1 and 3, all of the fatal cases developed azotemia

*Nitrogen Retention and Blood Pressure in Typhus* A lowering of the peripheral blood pressure was one of the characteristic features of the disease With the fall in systolic pressure a decrease in pulse pressure was often present Abnormal non-protein nitrogen concentrations were frequently noted in cases which had systolic blood pressures below 80 mm of mercury A subsequent rise in blood pressure was associated with decreases in the level of the non-protein nitrogen and an increase in the output of urine (chart 4)

A sudden fall in blood pressure from previously observed values was associated with the onset of azotemia in many cases (charts 5, 6, 7, 8) The level to which the blood pressure fell did not appear at times to be as significant as the degree of decline over previous levels In case No 5133, for example, a decrease in systolic pressure from 130 mm to 88 mm of mercury in 48 hours was associated with a rapid rise in blood non-protein nitrogen We have frequently observed blood pressures between 80 mm and 90 mm of mercury during the acute phase of typhus, however, with no rise in non-protein nitrogen or decrease in urine volume

It was our observation that as a group the patients with nitrogen retention did not show an average daily blood pressure lower than the group of patients without nitrogen retention (table 4) Sudden brief fluctuations appeared to be of most significance

TABLE IV  
Average Daily Blood Pressure Readings in 64 Cases of Typhus Fever during the  
Febrile Period of Hospitalization \*

|                                  | Number of<br>Cases | Average Daily Blood<br>Pressure |
|----------------------------------|--------------------|---------------------------------|
| Cases with no nitrogen retention | 31                 | 101/60                          |
| Cases with nitrogen retention    | 18                 | 101/66                          |
| Fatal cases                      | 15                 | 100/65                          |

\* Footnote as in table 1.

*The Degree of Nitrogen Retention and the Severity of the Clinical Course* In general it was observed that the degree of azotemia as measured by the elevation of the blood non-protein nitrogen was correlated with the severity of the clinical course of typhus fever Table 5 shows the range of the highest levels of the blood non-protein nitrogen recorded in each case with the average of the maximum values for each group of cases, classified according to the severity of disease Although there is considerable overlapping of non-protein nitrogen values between the groups of cases, it is apparent that in general the highest blood non-protein nitrogen levels were found in the most severely ill patients

*The Relationship between Nitrogen Retention and the Output of Urine* It has been difficult to obtain precise data on the output of urine in many

of our patients. Incontinence is common during the course of typhus, particularly during the critical second week of the disease. Although catheterization was done on many of our patients, it was not possible to anticipate incontinence in every instance. Special nursing procedures served to reduce the volume of urine lost.

TABLE V

The Concentration of the Blood Non-Protein Nitrogen Compared with the Severity of the Clinical Course of Typhus Fever

| Classification of Severity* | Number of Patients | The Range of Maximum Values for Blood Non-Protein Nitrogen of the Patients in Each Classification | Average of the Maximum Concentration of Blood Non-Protein Nitrogen in Each Classification |
|-----------------------------|--------------------|---|---|
|                             |                    | mg per 100 c c.   | mg per 100 c c  |
| "C"                         | 4                  | 47-74   | 58  |
| "D"                         | 9                  | 58-117  | 69  |
| "E"                         | 5                  | 72-162  | 92  |
| "F"                         | 14 †               | 75-200  | 120   |

\* Footnotes as in tables 1 and 2

† In one of the 15 fatal cases the blood urea nitrogen only was determined, the value was 150 mg per 100 c c

The development of nitrogen retention was frequently associated with a definite decrease in the output of urine, particularly in the cases which had a sudden decrease in blood pressure (charts 5, 6, 7, 8). On admission to the ward, critically ill patients with azotemia sometimes showed a low output of urine, associated with low 24 hour urine specific gravities, and low blood pressure (chart 4). In certain cases, for example case No 5769, the decrease in fluid intake and the rise in the specific gravity of the 24 hour urine output indicated that the lowered urine volumes observed under these conditions were due probably in large measure to the decreases in fluid intake. In other cases cited above decreases in the output of urine did not appear to be as closely associated with decreased fluid intake as with a fall in blood pressure.

In patients whose 24 hour urine outputs ranged above 2000 c c during the febrile period, nitrogen retention was rarely observed.

An additional observation of considerable importance with relation to renal function in typhus was the presence or development of a low, or comparatively low, specific gravity of the 24 hour urine specimens in the majority of cases with azotemia and low urine volumes (charts 3, 4, 5, 7, 8, 9, 10). Consideration of these findings is reserved for the *Comment*.

*Nitrogen Retention and Its Association with Dehydration* Abnormal concentration of the blood non-protein nitrogen is a common observation in typhus patients who demonstrate evidence of dehydration by physical examination, by observations on the output of urine, or by determination of the plasma protein and hematocrit. In such cases dehydration may be of considerable importance in the development of azotemia.

In a simultaneous study of 14 Cordon patients and 12 Commission ward

patients it was found that dehydration was present in nine of the former group and in two of the latter group. Azotemia was present in 13 of the 14 Cordon patients and in four of the 12 Commission ward patients.

Although the output of urine in the case of the Cordon patients could only be estimated, these differences in the incidence of nitrogen retention between the Cordon and Commission ward patients were believed due, for the most part, to emphasis placed on fluid intake in the care of patients in the Commission ward and the consequently large daily urine volumes in the latter group.

The concentrations of blood non-protein nitrogen in Cordon patients dying of typhus were much higher in general than on the Commission ward. Studies of the plasma proteins and hematocrit levels showed a steady increase in values up to the time of death. In one fatal Cordon case the concentration of the plasma proteins rose in 11 days from 7.0 gm per 100 cc to 11.5 gm per 100 cc 48 hours before death. During the same period the blood non-protein nitrogen rose from 141 mg per 100 cc to 277 mg per 100 cc. In this case, as in many another seen in the Cordon, there was no doubt that insufficient fluid intake with a consequent reduction in the output of urine was of great importance in the degree of azotemia observed.

The clinical features of typhus predispose to dehydration to such an extent that it is difficult to combat the development of this condition with the best nursing facilities available in typhus areas. This difficulty is found particularly in the critically ill cases. It is doubtful whether dehydration played a significant part in the initiation of nitrogen retention in a number of the fatal cases observed on our ward, but as the disease progressed a reduction in urine volumes with an increase in urine specific gravity indicated that dehydration was present and probably contributed to the increase in nitrogen retention which occurred.

*Nitrogen Retention and Nephritis in Typhus* Albuminuria was present in all patients during the febrile period of the disease, and in many instances persisted for some weeks during the period of convalescence.

Red cells and white cells were frequently noted in the sediment, often in large numbers. Frequent catheterization and the high incidence of Bilharzia in our patients, however, do not permit one to interpret the presence of red cells and white cells as evidence of nephritis. Infrequent examinations of the urine may not disclose the fact that a patient has Bilharzia. Daily examination of the concentrated urine sediment may show eggs in but a single urine specimen over a period of weeks. Cellular elements in the urine sediment of all our cases must, therefore, be interpreted with considerable caution.

Cellular casts were rarely seen. A notable exception was case No. 1109. The course of events in this patient's illness is considered in detail in the *Comment*.

The finding of numerous granular casts in the urine sediment was associated with azotemia in many cases. In some instances the number of casts

seen in the microscopic field appeared to vary indirectly with the urine volume. On occasions, however, this relationship was not clear-cut (chart 5). Rarely were granular casts absent at the time of death (charts 5, 8).

In summary it may be said that there was no conclusive evidence that typhus had produced acute glomerular damage leading to hematuria. There was, however, evidence for tubular damage in many cases which developed azotemia.

*Residual Impairment of Kidney Function Associated with Typhus Fever*  
Follow-up studies on our cases with severe nitrogen retention are too few to enable us to state definitely whether or not residual impairment of kidney function is a sequel to apparent severe renal insufficiency in typhus.

Two patients admitted to the Commission ward in 1943 developed severe renal insufficiency associated with oliguria and low urine specific gravities, hypotension and azotemia. They were "E" cases. At the time of discharge from the hospital, the concentrating power of the kidneys appeared normal. Albuminuria was intermittent. Twelve months following their illness, the physical examination was negative. Observation of the urine sediment, as well as the concentration-dilution test of renal function and urea clearance showed no evidence of renal disease or impairment of kidney function.

Two additional "E" cases were observed in follow-up studies for nine months to 15 months after their disease. These patients showed albuminuria, hyaline and granular casts in the urine sediment. They were unable to concentrate the urine above 1.018 on the overnight concentration test. The urea clearance was determined in one of the cases and found to be normal. One of these cases, No. 1109, was found to have a slight elevation of his diastolic blood pressure under resting conditions. No history of previous renal disease or infections resulting in possible renal disease could be obtained from these patients. However, the possibility of renal disease existing before the onset of typhus cannot be excluded.

Numerous patients on the Commission ward who were classified as "C" or "D" patients and who showed nitrogen retention, albuminuria and cylindruria during the acute phase of the disease, showed no impairment of kidney function at the time of discharge from the hospital as evidenced by examination of the urine sediment and specific gravity. In a number of these cases the urine was examined in follow-up visits and found to be negative. Our experience to date has shown that residual renal damage was not found after recovery from severe typhus with nitrogen retention except in two cases. In these patients, renal disease may have been present prior to the onset of typhus.

*Presentation of Cases\** The cases described below illustrate some of the phenomena associated with nitrogen retention in typhus. All of these

\*The determinations of the blood non-protein nitrogen, urea nitrogen and creatinine were done by the methods given in War Department, Technical Manual 8-227, "Methods for Laboratory Technicians," U. S. Government Printing Office, October 1941.

The determinations of the serum proteins were done by the method described by J. S. Simmons and J. C. Gentzkow, "Laboratory Methods of the United States Army," Lea and

patients were studied on the Commission ward. The clinical records are summarized, and charts have been included to illustrate the important data.

### CASE REPORTS

*Case No 5508*, male, age 25, "D" severity, was admitted on the fourth day of disease with the complaints of severe headache, pain in the back and knees. The day following admission the physical examination was as follows: Temperature 40.5° C, p r Pulse 120, Respirations 42, Blood pressure 106 mm Hg systolic and 68 mm diastolic, Weight 148 pounds. The patient was well-developed and muscular. His mental state was dull. There was no deafness. An extensive maculo-papular rash was present, covering the body from the neck to the feet. A few petechial spots were seen on the inner surface of one arm. The eyelids appeared edematous. The conjunctivae were lightly suffused. The tongue was moist and white coated. A few coarse rhonchi were heard over both lower lung fields. There was no cardiac enlargement to percussion. The heart sounds were of low intensity. The rate was rapid, the rhythm regular. No murmurs were heard. The spleen was felt to descend 3 cm below the costal margin and was not tender.

*Admission laboratory data* Hemoglobin 89 per cent ( $\text{CuSO}_4$ ), red blood cells 4,320,000, white blood cells 1,900 with 71 per cent polymorphonuclear cells. Urine dark amber in color, cloudy, reaction acid, specific gravity 1.018, albumin 2+. A few squamous epithelial cells, 20-25 white blood cells, a rare red blood cell and 1-2 granular casts per low power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 41 mg per 100 cc. The urea clearance was 86 per cent of normal. The serum proteins were 6.9 gm per 100 cc, albumin 4.1 gm per 100 cc, globulin 2.8 gm per 100 cc. The roentgenogram of the chest showed small shadows scattered throughout both lung fields. The electrocardiogram was within normal limits.

*Hospital course* (chart 1) The patient ran a severe course of typhus with continuous fever for 26 days. From the fourth day to the eleventh day of disease constant sponging was employed in an attempt to reduce the fever. The rash increased, the face became dusky, the conjunctivae very injected. He developed extreme deafness, delirium, a stammering speech, and tremors of the extremities. An apical gallop

Febiger, 1944, p. 221. Roentgenograms were taken with a portable Picker U. S. Army Field Unit. Electrocardiograms were taken with a Cambridge "Simpli-trol" Portable Electrocardiograph. In many cases, the values for plasma proteins, hemoglobin, and hematocrits were determined by the method of R. A. Phillips, D. D. van Slyke, V. P. Dole, K. Emerson, Jr., P. B. Hamilton, and R. M. Archibald, "The Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma," *Bureau News Letter*, Navy Department, Vol. I, No. 9, June 25, 1943.

Catheterization was done for all urea clearance tests on febrile patients. The method of Technical Manual 8-227 was used for the determination of urine urea nitrogen. The calculation of the urea clearance followed the method of E. Moller, J. F. McIntosh and D. D. van Slyke as presented by Peters and van Slyke, "Quantitative Clinical Chemistry," Vol. II, 1943—Methods, p. 564-572.

In the case reports the term " $\text{CuSO}_4$ " following the values for hemoglobin signifies that the hemoglobin concentration was measured by the copper sulphate method of Phillips et al. (see above).

The numbers at the top of the chart refer to days of disease. The temperature is recorded rectally in degrees Centigrade. A temperature of 37.5° C or above was considered as evidence of fever. Plasma protein determinations, charted as per cent of normal, were done by the method of Phillips and his co-workers (see text). The letter "P" over the fluid intake column signifies that a part or all of the fluid intake was by parenteral route on that day. The plus mark over the fluid output column signifies that a part of the 24 hour urine output was lost. The letters "CP" indicate that catheterization was used to obtain part or all of the 24 hour output of urine.

This footnote also applies to Charts 2 through 10.



rhythm was noted on the eighth day of disease. He became incontinent of urine and feces on the tenth day. Between the eleventh and the fourteenth day the patient developed urinary retention and thereafter was put on constant bladder drainage for seven days.

Throughout the second hospital week (from the eleventh to the seventeenth day of disease) the mental status of the patient remained the same. He was at times stuporous, at other times quietly delirious, completely oblivious of his surroundings. Speech was almost unintelligible. Words were run together and stammering persisted. Jerky, trembling movements of the arms and legs were present for the greater part of this time. However, it was possible to keep up his fluid intake without resorting to parenteral administration. His blood pressure continued to be well-maintained.

On the fifteenth day his temperature began to fall. There was no cough. Slight dullness to percussion and coarse râles were heard over the right upper chest posteriorly. A roentgenogram of the chest showed small, diffuse mottled shadows throughout both lung fields, particularly over the right upper lobe. On the sixteenth day the output of urine exceeded 5 liters.

The temperature slowly fell to normal between the seventeenth and the twenty-sixth day of the disease. A brief rise on the twenty-third and the twenty-fourth day was attributed to a urinary tract infection. The rash had completely faded out by the twenty-second day of the disease. Serial electrocardiograms taken during the first five weeks of hospitalization showed at times T-waves of borderline amplitude in Leads I and II.

His mental state slowly improved and appeared normal at the time of discharge. The patient lost over 31 pounds in weight during his illness and was 20 pounds underweight when he left the hospital 55 days after onset of disease. During hospitalization ova of *Schistosoma haematobium* were found on several examinations of the urine sediment.

On follow-up examination three months after onset of typhus the patient was still 11 pounds under his normal weight, complained of slight residual tinnitus and weakness in his legs. Physical examination was essentially negative except for slight objective deafness and persistent weight loss. A mild anemia was present. His urine contained many pus cells and a very slight trace of albumin. There was no evidence of diminution in renal function.

*Case No 5808*, male, age 25, "E" severity, was admitted on the sixth day of disease with the chief complaint of headache. The important findings on physical examination were as follows: Temperature 40.7° C p r. Pulse 108. Respirations 36. Blood pressure 126 mm Hg systolic and 66 mm diastolic. Weight 121 pounds. The patient was moderately well-developed and nourished. He appeared mentally clear and not acutely ill. No tinnitus or deafness was present. The skin was dark. No evidence of a typhus rash was seen. The conjunctivae were negative. The tongue was white coated and moist. The chest was clear to percussion and auscultation. Examination of the heart showed nothing remarkable.

*Admission laboratory data:* Hemoglobin 83 per cent ( $\text{CuSO}_4$ ), red blood cells 4,500,000, white blood cells 7,550 with 81 per cent polymorphonuclear cells. Urine: amber in color, cloudy, reaction acid, specific gravity 1.028. A few squamous epithelial cells, 1-2 granular casts per low power field, 1-3 white blood cells per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 46 mg per 100 cc. The plasma proteins were 6.8 gm per 100 cc.

*Hospital course* (chart 2). Throughout the first week of hospitalization the patient's fever remained high and the rash appeared with intense conjunctival injection, the development of petechiae in the left conjunctival sac, and active delirium. The patient became very talkative and attempted to get out of bed. Intake by mouth continued satisfactorily until the twelfth day of disease. It was necessary thereafter

AZOTEMIA IN TYPHUS FEVER

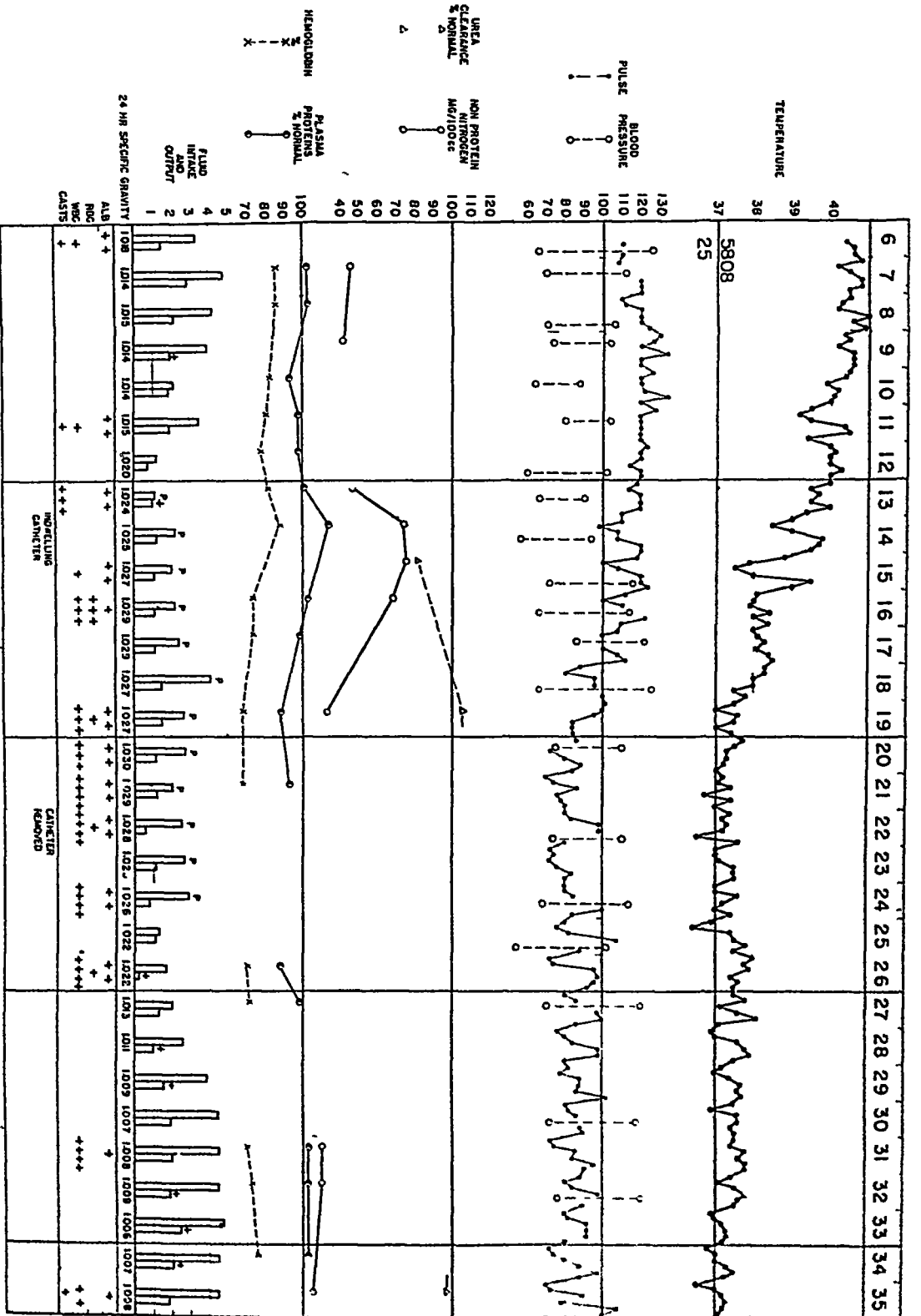


CHART 2 Case No 5808



to resort to subcutaneous injections of 5 per cent dextrose in saline and normal saline for the next 12 days

On the thirteenth day of disease he became more stuporous and then semicomatose. He lay with half opened eyes, breathing quietly. Facial grimaces and grinding of the teeth were present. Fluid intake by mouth practically ceased. He was put on constant bladder drainage on this day because of urinary retention. His condition remained much the same from the thirteenth to the seventeenth day of disease. The rash gradually faded out during this period of time and the conjunctival suffusion disappeared.

On the seventeenth day slight improvement was noted in his mental state. He stared about the ward, his mouth open in a wide grimace. When spoken to he replied in a series of unintelligible whining sounds. There was no indication that he recognized people. The rash was no longer visible.

In the next two days he was able to obey simple commands. It was evident that he was almost totally deaf. On the twentieth day his temperature reached normal levels. Examination showed hyperactive knee jerks and ankle jerks but normal plantar response. An area of skin necrosis appeared over the coccyx.

On the twenty-second day the catheter was removed. When he was spoken to it was obvious that he was attempting to reply, but he could not articulate and the facial expressions were similar to those of a crying baby.

The area of necrosis over the lower back continued to enlarge. The patient was placed in a chair on the twenty-fourth day. A low grade fever continued. He was by that time able to eat solid food and the oral fluid intake gradually increased.

On the twenty-seventh day the patient was found to have not only hyperactive knee and ankle jerks but a bilateral positive Babinski reaction. Voluntary motion of the extremities was uncoordinated.

From this time onward improvement in his general condition was steady but slow. The ability to stand and walk unassisted returned before the ability to form words. At the time of discharge 68 days after the onset of the disease, the lesion over the coccyx was healed. Speech was slow, expressionless and labored. Hyperactive reflexes were still present in the lower extremities, but the positive Babinski phenomenon had disappeared.

On the follow-up examinations during the next four months the patient showed progressive improvement. Mentally he appeared alert. There was no residual deafness. The reflexes in the lower extremities remained hyperactive, however, and speech was still slow, labored, and monotonous in tone. Examination of the urine showed normal concentrating power, no albumin and a negative urine sediment. The anemia which had developed during the disease was no longer present.

*Case No 1109*, male, age 35, "E" severity, was admitted on the tenth day of disease with the chief complaints of headache and buzzing in the ears. The important findings on physical examination were as follows: Temperature 39.0° C p r. Pulse 98. Respirations 40. Blood pressure 96 mm Hg systolic and 66 mm diastolic. Weight was not determined. The patient appeared well-developed, objectively deaf, and dis-oriented. He had no cough. A macular rash was present, extending from the neck to below the knees and involving the arms to the wrists. Some macules were fixed, others blanched on pressure. In some areas the rash appeared petechial in character. The skin of the face appeared dusky. The conjunctivae were not suffused. The tongue and oral mucous membranes were moist. The lungs were clear. There was no cardiac enlargement to percussion. Heart sounds were well heard, and the action was regular. There were no murmurs. The liver and spleen were not palpable. The extremities were negative. The deep tendon reflexes were normal.

*Laboratory Data*: Hemoglobin 96 per cent (Sahli). Red blood cells 1600000. White blood cell 5000 with 83 per cent polymorphonuclear cells. Urine

amber in color, cloudy, reaction alkaline, specific gravity 1.010, albumin 2+, an occasional red blood cell and epithelial cell were seen in the centrifuged sediment. The blood non-protein nitrogen was 86 mg per 100 c.c. The plasma proteins were 6.5 gm per 100 c.c.

The electrocardiogram showed low voltage of the QRS complexes.

*Hospital course* (chart 3) The patient ran a stormy course of typhus. The rash increased during the 24 hours after admission, thereafter it began to fade, and disappeared by the twenty-seventh day of illness. He was incontinent of urine and feces during the first 10 days of hospitalization. The day following admission (the eleventh day of the disease) he was more delirious, conjunctival injection increased, and the face became quite dusky. He developed continuous twitching of the upper extremities and marked distention of the abdomen.

On the thirteenth day he was stuporous but not comatose. There was occasional twitching of the facial muscles as well as of the arms. The neck was somewhat resistant to passive flexion. An occasional rhonchus was heard over the lungs. The heart borders could not be definitely determined by percussion, and the heart sounds were obscured by phonation. An apical gallop rhythm was believed present. Abdominal distention was absent. He showed hyperactive reflexes in the lower extremities with a well-sustained bilateral ankle clonus.

During the next 48 hours his condition grew steadily more critical. Jerky movements of the facial muscles, the arms and occasionally the legs continued. The dusky hue to the face remained, but the conjunctivae showed less suffusion. The heart rate continued rapid, and a loud apical gallop rhythm was heard. The tendon reflexes in the lower extremities were still hyperactive. On the fifteenth day the electrocardiogram showed low T-waves in Leads I and II.

From the sixteenth to the nineteenth day of disease his general condition remained the same. Incontinence and deep stupor persisted. He was able to take fluids slowly by mouth. However, intravenous and subcutaneous injections of 5 per cent dextrose in saline were given to supplement the oral fluid intake.

Lumbar puncture on the twenty-first day showed a pressure of 120–130 mm with normal dynamics. The spinal fluid was clear with 9 cells per cu. mm.

On the twenty-second day he appeared to hear when spoken to but was unable to reply except by low wails. A loose cough was present, but no sputum was obtained. Considerable lateral divergence of the right eyeball was noted for the first time. The neck was quite resistant to passive flexion. The lung fields were clear. A rough, scratching to and fro murmur was heard in the third and fourth interspace to the left of the sternum. The heart rate was still rapid, an apical gallop rhythm was present. The extremities showed considerable wasting, and there were periodic coarse tremors of both legs. The tendon reflexes in the extremities were quite hyperactive, a well-sustained ankle clonus was present. The Babinski, Gordon, and Oppenheim reactions were negative. At this time the outlook still appeared to be poor.

However, during the next four days, twenty-second to the twenty-fifth day of disease, a slow but definite improvement was noted. He became more cooperative, and could open his mouth for examination. He was even able to say a few words and ask for the bed pan, but his speech was little more than the wail of a baby. It seemed as though he were trying to learn to talk all over again. During the day he lay quietly with eyes open, his face expressionless. The precordial friction rub was still present and other physical signs remained the same.

On the twenty-seventh day of disease he complained of cramp-like abdominal pain which was poorly localized. The white cell count on this day was 5,700 with 78 per cent polymorphonuclear cells. The urine showed many white cells, red cells, hyaline, granular and cellular casts.

On the twenty-ninth day of disease the patient appeared worse. He was pale, dyspneic, and orthopneic. In the 45° sitting position the neck veins were not distended. Examination of the heart revealed no enlargement on percussion. The heart sounds were very faint. The rate was 140-150 beats per minute. The rhythm was regular. No murmurs were heard. The lungs were clear. The abdomen was not distended, but was resistant to palpation. The liver and spleen were not felt. There was definite pitting edema over the dorsum of the feet but none over the sacral area. The systolic blood pressure had steadily decreased during the previous 72 hours and the output of urine had likewise diminished. An electrocardiogram taken the twenty-eighth day showed continuing low voltage with inverted T-waves in Lead I and flattened T-waves in Lead II. Digitalization was begun on the evening of the twenty-ninth day.

On the thirtieth day the patient was given a transfusion of 500 cc of citrated blood.

Gradual improvement was noted during the next three days. The dyspnea and orthopnea disappeared, and the ankle edema decreased. On the thirty-second day the electrocardiogram showed inverted T-waves in Leads I and IV and diphase in Lead II, with low voltage. On the thirty-third day he was put on a maintenance dose of digitalis of 0.1 gm daily until the fifty-first day, when the drug was discontinued.

On the thirty-fifth day a purulent discharge was noted coming from the left ear and examination revealed a perforation of the drum. He was given sulfathiazole for five days and the discharge from the middle ear ceased on the forty-first.

On the thirty-ninth day of disease he developed redness of the skin and edema of the left upper cheek and the lids of the left eye, which persisted for 48 hours.

On the forty-first day the edema of the feet was no longer present. At this time his mental condition had improved remarkably, though he still was childish in his reactions and quite deaf. He was gaining weight. The tremor and twitching had ceased, but the reflexes were still hyperactive. Examination of the heart revealed no abnormalities. The electrocardiogram showed the T-waves in Lead I to be more deeply inverted than on the thirty-second day.

On the forty-eighth day after onset of typhus he was allowed up in a chair. On the fifty-seventh day the T-waves in Leads I and II were more deeply inverted with slight depression of the S-T level, suggestive of digitalis effect.

Two months after the disease onset the urine continued to show albumin, red cells, white cells and cellular casts. The eye grounds were first satisfactorily examined on the sixty-first day. The discs appeared normal. The arterioles were narrowed and white streaked. Arteriovenous compression and hemorrhages were not seen.

The patient was discharged from the hospital on the seventy-first day after the onset of typhus fever. It was estimated by his family that he was still 15 pounds under his normal weight. He was still quite deaf and tinnitus was present. Mentally he appeared normal. The physical examination showed nothing remarkable except for hyperactive reflexes in the lower extremities. The blood pressure was 126 mm Hg systolic and 84 mm diastolic. The red cell count was 3,000,000. The urine concentration-dilution test showed the inability to concentrate above 1:015 or to dilute below 1:005. The urea clearance was 117 per cent of normal, however. During convalescence ova of *Ascaris lumbricoides* and *Ankylostoma duodenale* were found repeatedly in the stools.

On follow-up examinations over a period of nine months the patient appeared in the best of health except for slight residual bilateral deafness and tinnitus. His mental state appeared to us and his family to be entirely normal. He still had residual weakness of the extrinsic muscles of the right eye. Hemoglobin values were between 90 and 100 per cent. His red cell count remained above 4,000,000. His blood pres-

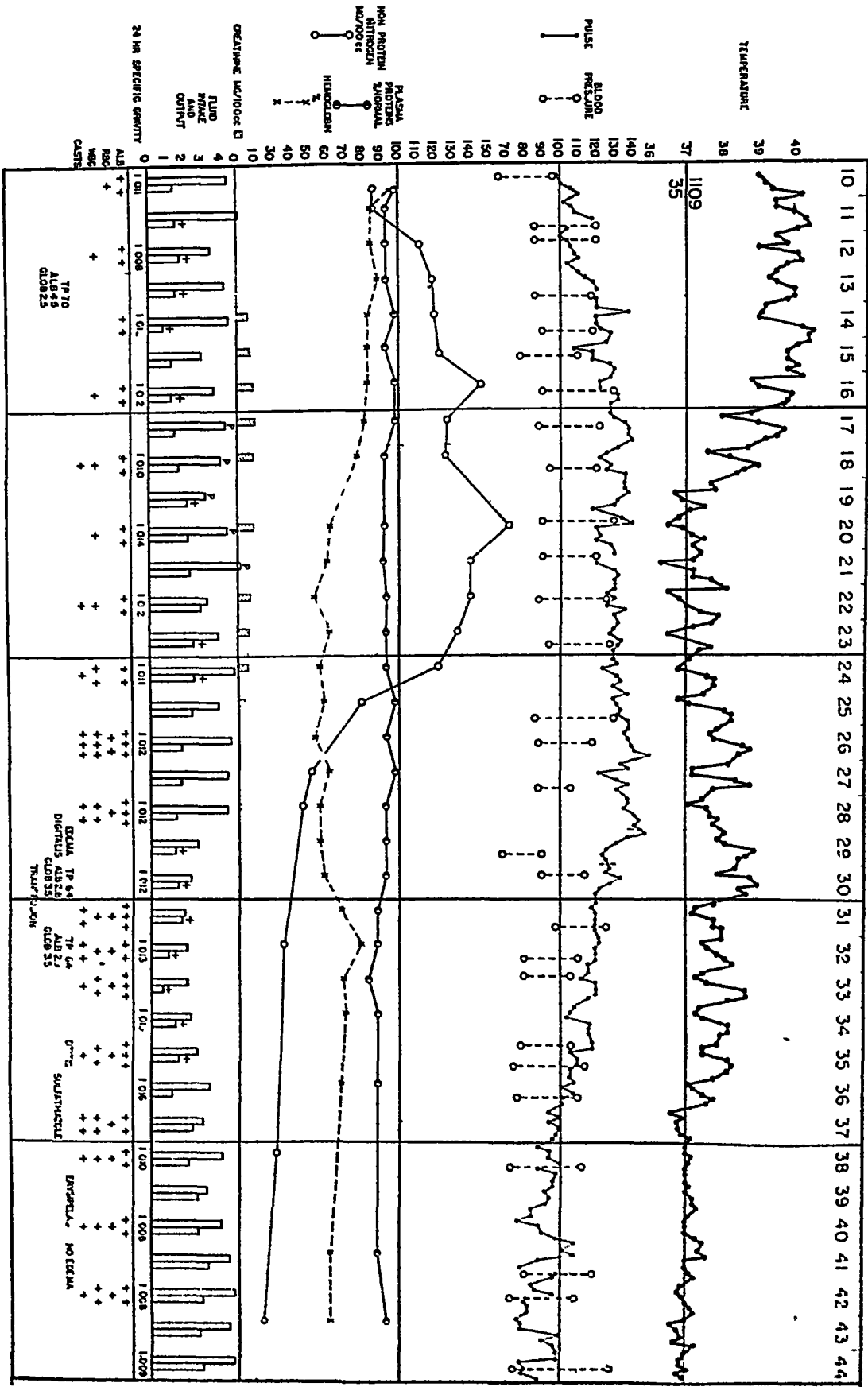


CHART 3 Case No 1109

sure under basal conditions varied between 128 mm Hg systolic and 80 mm diastolic to 140 mm Hg systolic and 96 mm diastolic. Repeated urine concentration tests of kidney function showed inability to concentrate the urine above 1017.

Six months after the onset of typhus the electrocardiogram showed T-waves of low amplitude in Lead I and inverted in Lead II. Nine months after the onset of the disease the T-waves in Lead I were normal but remained inverted in Lead II.

*Case No 4690*, male, age 45, "E" severity, was admitted on the eleventh day of disease with the chief complaint of headache. The important findings on admission physical examination were as follows. Temperature 40.0° C p. Pulse 110. Respirations 38. Blood pressure 68 mm Hg systolic and 40 mm diastolic right arm, 74 mm Hg systolic and 58 mm diastolic left arm. Weight was 121 pounds. The patient was well-developed and in no respiratory distress. He was mentally clear, but drowsy. There was no objective deafness. A diffuse macular rash was present over the back, sides of the chest, and upper legs. The macules were small (2-3 mm in diameter) and blanched on pressure. The pupils were constricted and reacted sluggishly to light and on accommodation. Three small petechial hemorrhages were seen in the right conjunctival sac. The conjunctivae were slightly injected. The tongue was moist with a light brown coat. The oral mucous membranes were moist. Several dark red petechial lesions were seen on the soft palate. There was slight dullness at the right lung base posteriorly. Coarse rhonchi were heard over both bases. The heart showed no enlargement on percussion. The first sound at the apex was of low intensity. The action was regular. No murmurs were present. The abdomen was slightly distended. The spleen tip was questionably palpable. The reflexes were depressed.

*Admission laboratory data*. Hemoglobin 83 per cent (Sahli). Red blood cells 4,130,000, white blood cells 10,950 with 85 per cent polymorphonuclear leukocytes. Urine dark amber in color, cloudy, reaction acid, specific gravity 1.011, albumin 2+, 3-4 granular casts per low power field, 4-6 white blood cells and a rare red blood cell per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 59 mg per 100 cc. The urea clearance was 50 per cent of normal.

*Hospital course* (chart 4). The patient was admitted with a low blood pressure, but the extremities were warm and the radial pulses easily palpable. Repeated catheterization was required during the first three hospital days because of urinary retention.

On the thirteenth day he became incontinent of urine and feces. Coarse rhonchi and râles were present throughout both right and left lower lobes. Disorientation continued. The blood pressure remained low, but the extremities were warm and the radial pulses full. The outlook at this time was poor.

On the fourteenth day his general condition appeared worse. He was semicomatose. A loose cough was present, but no sputum could be obtained. Fresh petechial hemorrhages appeared in the conjunctival sacs. The tongue was moist with a brownish coat. Coarse râles were heard throughout both lower lung fields. The heart sounds were not well heard owing to phonation. The abdomen was negative. The radial pulses were soft with occasional dropped beats. The rash was still very evident. There was no edema. An electrocardiogram showed occasional ventricular extrasystoles with abnormally low QRS and T-waves of low amplitude in Leads I and II. A roentgenogram of the chest showed increased lung markings throughout both lung fields. The patient was given 2,000 cc of 5 per cent dextrose in saline subcutaneously. The prognosis remained poor.

On the fifteenth day he was still extremely stuporous, but responded slightly to commands and needle pricks. He was voiding spontaneously and able to take small amounts of fluid by mouth. The rash had increased in intensity. There were no other changes in physical examination from the previous day. He was given 1,000 cc of 5 per cent dextrose saline subcutaneously.

On the sixteenth day he appeared definitely improved slowly to questions, and was taking more fluids by mouth He was voiding satisfactorily, though incontinent He was able to respond He appeared to be quite deaf The blood pressure had risen considerably

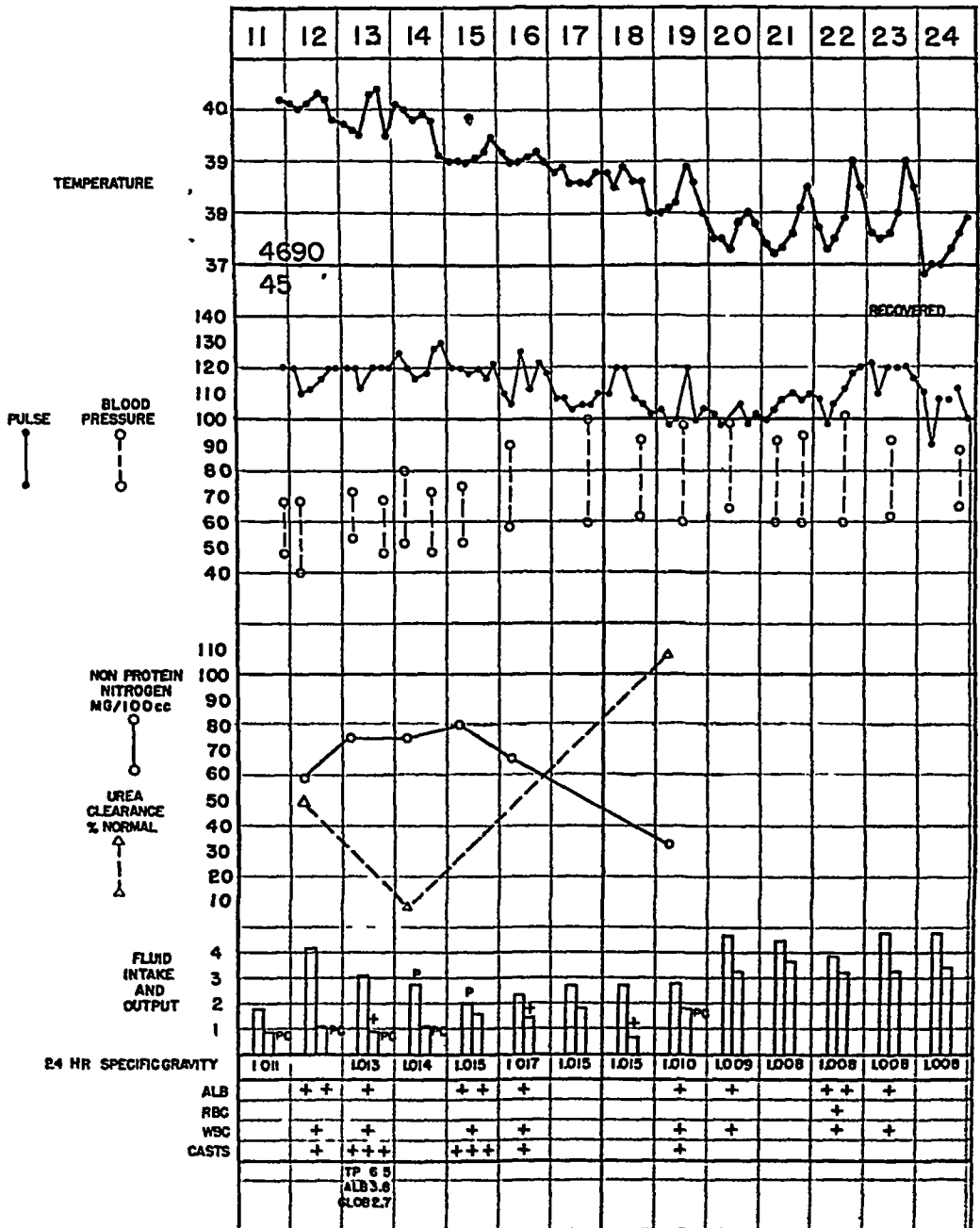


CHART 4\* Case No 4690 .

\* In chart 4 the value for the urea clearance on the fourteenth day of disease is incorrectly charted as 8 per cent of normal. The true value obtained was 25 per cent of normal.

Improvement in his general condition continued in the next 48 hours. At times he was incontinent of stools. Mentally he appeared brighter, but for the most part lay quietly, with an apathetic expression. The cough was still present and he was raising small amounts of white sputum. The face became lighter in color, conjunctival suffusion had disappeared and the conjunctival petechiae were fading. The tongue appeared more moist. There was percussion dullness at both lung bases with fine inspiratory râles over both lower lobes. The heart and abdomen were without significant findings. The extremities appeared slightly spastic to passive motion. The reflexes appeared normal. The rash was rapidly fading.

Improvement from the eighteenth day onward was rapid. He continued to run a low grade swinging fever until the twenty-eighth day after the onset of his disease. This was associated with a cough and slowly resolving signs of pulmonary congestion over the right lower lobe, the development of a small area of skin necrosis over the tip of the coccyx, and furunculosis of the scalp. On the twentieth day of disease an electrocardiogram showed T-waves flattened in Lead I and inverted in Lead IV. On the twenty-fifth day after onset of the disease the T-waves in Lead I again became upright but of low amplitude. On the thirtieth day the T-waves in Lead I were still of low amplitude but were normal in Leads II and IV. At the time of discharge from the hospital, the thirty-seventh day after onset, he was still 14 pounds under his admission weight. The tip of the spleen was barely palpable. The urine contained no albumin, but many white cells.

On follow-up examination one month after discharge the patient had gained 12 pounds in weight but was still two pounds under his weight at the time of his first admission. He had been working steadily and had no complaints. The physical examination was negative. His blood pressure was 96 mm Hg systolic and 68 mm diastolic. He appeared in the best of health.

Two and one-half months after his discharge he returned again for 10 days of follow-up examinations. At this time he weighed 124 pounds. The physical examination was negative, the blood pressure 90 mm Hg systolic and 60 mm diastolic. His blood count was normal. Repeated urine examinations at this time showed no albumin and a negative sediment. The urine specific gravity ranged between 1.002–1.018. The blood non-protein nitrogen was 25 mg per 100 c c.

*Case No. 3307*, male, age 36, fatal case, was admitted on the fifth day of illness with the chief complaints of headache, pain in the legs and back. Physical examination on admission was as follows: Temperature 40.5° C p r. Pulse 116. Respirations 34. Blood pressure 124 mm Hg systolic and 68 mm diastolic. Weight 132 pounds. The patient appeared well-developed, moderately well-nourished, and acutely ill. He was mentally alert. There was no objective deafness. There was a nonproductive cough. Examination of the skin showed a macular rash, distributed over the back, upper chest, buttocks and thighs. A few isolated macules were seen on the arms. The macules were light pink in color, blanched under pressure, and developed very rapidly during the succeeding six hours after admission. The skin of the face was dusky. The conjunctivae were moderately suffused. The tongue was white coated and moist. A draining furuncle was present on the left side of the neck, below the hairline of the scalp. There were coarse inspiratory and expiratory wheezes heard over both lower lung fields posteriorly. The heart was not enlarged to percussion, the sounds were of normal quality, the rhythm was regular and no murmurs were present. The abdomen was distended and tympanitic. No organs were palpable. There was no tenderness. The remainder of the physical examination was negative.

*Admission laboratory data.* Hemoglobin 85 per cent (Sahli), red blood cells 3,420,000, white blood cells 6,950 with 77 per cent polymorphonuclear cells. Urine: amber in color, cloudy, reaction acid, specific gravity not measured, albumin 3+, many granular casts, 15–20 white blood cells and occasional red blood cells were seen in the centrifuged sediment. The blood non-protein nitrogen was 28 mg per 100 c c.

The total serum proteins were 71 gm per 100 cc, albumin 43 gm per 100 cc, globulin 28 gm per 100 cc

*Hospital course* (chart 5). The patient had a high fever during the first three days of hospitalization, requiring frequent sponging to keep his temperature below 40.5° C. The rash continued to increase and he became progressively more stuporous

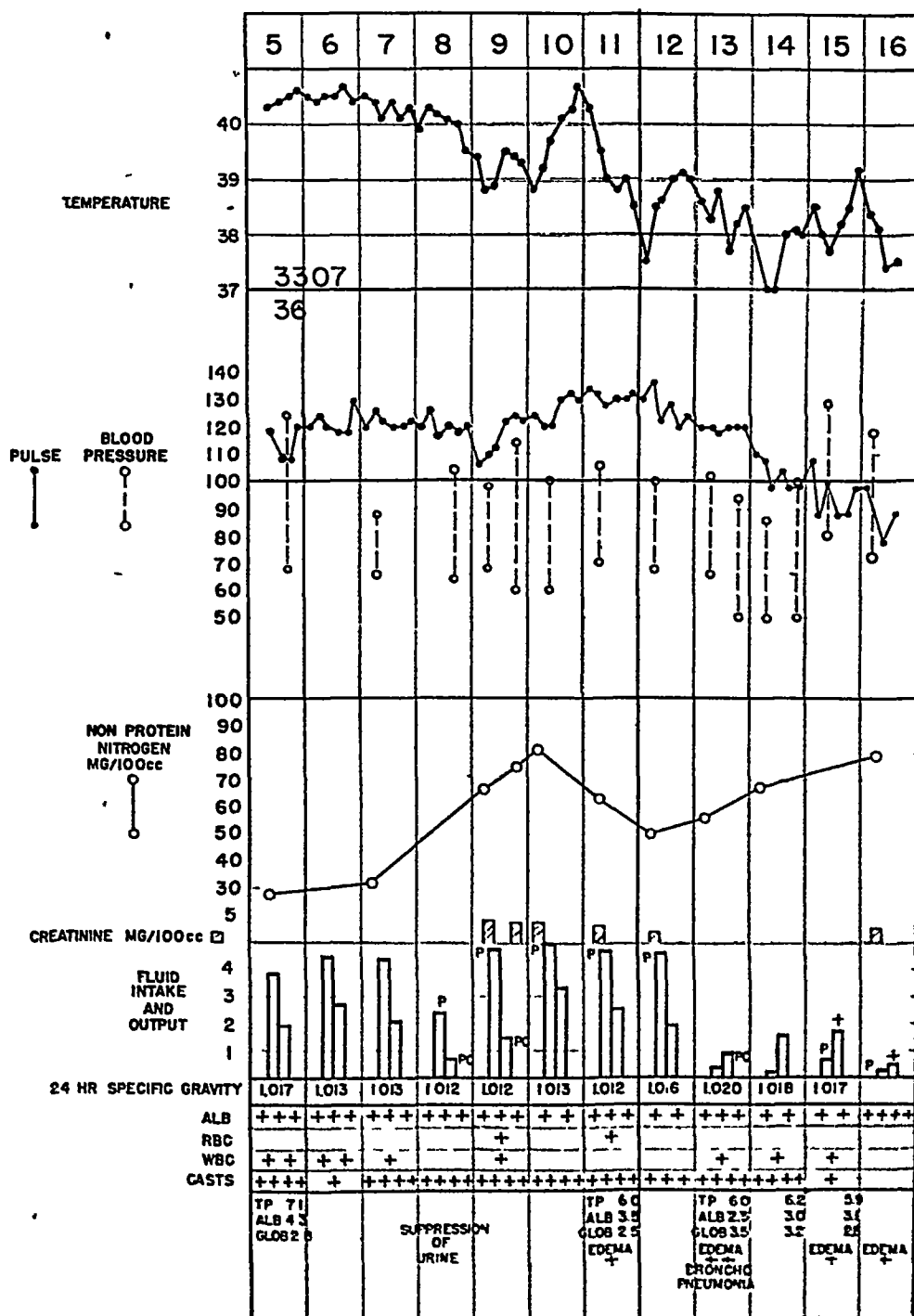


CHART 5 Case No 3307



On the evening of the seventh day he developed continual hiccoughs. On the eighth day his stupor had increased. It was difficult for him to take fluids by mouth. He had a cough productive of whitish sputum. He was disoriented. The face was dark blue in color. The conjunctivae showed considerable suffusion. The pupils were constricted and reacted sluggishly to light. The tip of the tongue appeared dry. The mucous membranes of the mouth were moist. The neck was not stiff. There were a few fine inspiratory râles at the left lung base. The area of cardiac dullness was not increased. The rhythm was normal. No murmurs were heard. The abdomen was slightly distended. No organs were palpable. There was no tenderness. The extremities were negative, the reflexes normal. The rash was now profuse and generally distributed over the back, chest, abdomen, arms, and legs. Numerous petechiae were present over the lower legs. The macules were of varying size, all appeared to blanch on pressure. The furuncle on the neck was draining satisfactorily. A roentgenogram of the chest showed small round shadows diffusely scattered throughout the lower left lung field. An electrocardiogram revealed QRS complexes of low amplitude. The patient did not void between 7:30 a.m. and 4:30 p.m. On catheterization 290 c.c. of dark amber, turbid urine were obtained. He was given 1,000 c.c. of 5 per cent dextrose in saline subcutaneously.

On the ninth day his stupor and delirium increased. The hiccoughs continued. There were occasional coarse tremors of the arms. The facial duskiness was more evident and the eyelids appeared puffy. The rash was more profuse. He was unable to void for the first 10 hours of the day. Four hundred and twenty-five c.c. of turbid urine were obtained by catheterization in the morning. He was given 4,000 c.c. of 5 per cent dextrose in saline by slow infusion during the day. At 4:00 p.m. he voided spontaneously and continued to do so during the night. A sputum specimen showed a moderate number of gram-positive and gram-negative cocci and diplococci. There were very few polymorphonuclear cells in the sputum smear.

On the tenth day there was slight improvement in his general condition. He was able to respond slowly to questions. His only complaint was hiccoughs. There was no essential change in the physical signs, save that many of the macules were becoming dark and fixed. The infusion of dextrose in saline was continued. The output of urine had increased and he was voiding well.

On the eleventh day he appeared sicker. The hiccoughs had lessened in frequency and severity, but his respirations had increased to 46 per minute. The cough was still present and the sputum had become purulent. The face was still very dusky. The pupils were constricted, and the conjunctivae were still suffused. The mucous membranes of the mouth were moist. Numerous hemorrhagic spots had appeared on the right buccal mucosa. There was no dullness over the lung fields to percussion, but coarse rhonchi were present throughout both lower lobes. There was no increase in the area of cardiac dullness. The heart sounds were strong. An apical gallop rhythm was present. The abdomen was not distended. The spleen was felt to descend 4 cm. on inspiration. The edge was soft and apparently not tender. The liver was not palpable. There was no twitching of the extremities. However, slight pitting edema of the feet was present. The reflexes were not abnormal. The sputum was yellowish, mucopurulent, and showed numerous polymorphonuclear cells with gram-positive diplococci and cocci in chains and a few pleomorphic gram-negative organisms. The white cell count was 12,150 with 80 per cent polymorphonuclear cells. A roentgenogram of the chest showed small discrete shadows which were diffusely distributed throughout both lungs, particularly in the lower half of each lung field.

On the twelfth day the patient appeared more alert. The hiccoughs ceased. The respirations appeared labored. There was slight dullness to percussion over the lower lung fields with coarse râles. The area of cardiac dullness was not increased. The rate was rapid and an apical gallop rhythm was still present. The abdomen was

slightly distended. There was no increase in edema over the previous day. An electrocardiogram showed increasingly low voltage of the QRS complexes with low amplitude of the T-waves in Leads I and II. A slow infusion of 3,000 cc of 5 per cent dextrose in saline was given. He was not able to take more than 100 cc of fluid per hour by mouth.

On the thirteenth day the patient's condition was much more critical. He was orthopneic. Respirations were 54 per minute, and tracheal râles were heard. There was no cough. The face was still dusky and the pupils constricted. The tongue appeared dry. There was dullness at the left lung base with coarse inspiratory râles and bronchial expiratory wheezes over both lower lung fields. The heart sounds were obscured by lung sounds, but an apical gallop was still detected. The abdomen was slightly distended and tympanitic. The pitting edema of the feet had increased. There was pitting edema of the thighs. The hands and feet were warm. There were no tremors.

The patient's condition grew rapidly worse throughout the morning. The tracheal râles became louder, the nail beds cyanotic. Postural drainage produced a considerable amount of frothy, purulent appearing material which on smear contained many polymorphonuclear cells and great numbers of gram-negative and gram-positive cocci. The patient was given oxygen by nasal catheter, 0.0015 gm of strophanthin "G" intravenously, and 10,000 units of penicillin intravenously followed by 150,000 units intravenously during the next 12 hours. Postural drainage was continued at intervals throughout the afternoon and evening. The edema increased throughout the day. There was considerable swelling of the lower back, the hands, and arms. By evening however, the cyanosis had lessened so remarkably that oxygen was discontinued. He was able to comprehend orders. An electrocardiogram taken five hours after the administration of strophanthin showed no changes from the tracing of the previous day. Intake by mouth during this 24 hour period was 400 cc.

On the morning of the fourteenth day the patient appeared slightly improved. Tracheal râles were still present but less audible than on the previous day. The respiratory rate and heart rate were decreasing. The patient was still quite stuporous, however. Examination of the lungs showed dullness over the left lower lobe posteriorly and in the left axilla. There was no increase in the area of precordial dullness. The heart sounds were strong, the rhythm regular, and no murmurs were heard. The abdomen was slightly distended without evidence of free fluid. The rash was becoming less evident. There was no decrease in the peripheral edema. He was given 0.001 gm of strophanthin "G" intravenously. The patient continued to void throughout the day and was tried on small amounts of fluid at intervals. However he appeared to experience considerable pain in swallowing. Examination of the mouth revealed large amounts of thin, gray, purulent material in the oropharynx. No focus was seen in the parts of the mouth or throat which could be examined. On smear this material showed numerous polymorphonuclear cells, a rare gram-positive coccus and diplococcus and a few gram-negative diplococci. Examination was difficult owing to the patient's resistance, but it appeared that the pus was originating from some focus lower in the pharynx, possibly the esophagus.

On the fifteenth day he was still extremely stuporous, coughing occasionally but apparently raising very little sputum. The respirations were deep and regular and 40 per minute. The examination of the chest revealed no changes. The blood pressure had risen considerably in the preceding 24 hours. A large dark bluish area was present in the skin over the lower sacrum. The patient was given 100 cc of concentrated human albumin intravenously followed by 50 cc of normal saline. The edema appeared to decrease throughout the day.

On the morning of the sixteenth day the patient was more stuporous and could hardly be roused. The respiratory rate was 40 per minute, the breathing quiet and

regular. An occasional loose cough was not productive of sputum. There was dullness over the left lower lung field to the lower border of the scapula with moist sounding râles, but no evidence of consolidation. A few râles were heard over the right lower lobe. The heart showed no evidence of dilatation, the sounds were strong, the rhythm regular. The abdomen was soft. The edema had decreased markedly since the previous day. The large bluish area of skin over the sacrum was still intact. He was given 250 c c of plasma intravenously in the morning. He gradually became more comatose throughout the day. Respirations ceased suddenly at 4 00 p m.

A postmortem examination was performed one and one-half hours after death by Lieutenant Commander W B McAllister, Jr, the important gross findings were as follows:

The body was that of a well-developed, well-nourished, light-skinned Egyptian male which weighed about 135 pounds. Rigor mortis was not present, and there was no jaundice. There was marked subcutaneous edema, all of the tissues were edematous, and there was some free fluid in all of the serous cavities. There was a diffuse macular and petechial cutaneous rash characteristic of typhus. Aside from a few pale areas in the myocardium near the epicardium, the heart was normal. The lungs, particularly the posterior portions, were congested, and in the lower lobes there were numerous small, reddish areas of early consolidation. There was a marked acute bronchitis and tracheitis. There were numerous petechiae in the buccal mucous membranes. A communication led through the socket of the left third molar, which was absent, into the left maxillary sinus. A large amount of tenacious purulent material drained from this tooth socket. Associated with this tract was another leading through the soft tissues of the lateral wall of the pharynx into a pocket which lay behind the posterior wall of the pharynx. All of the soft tissues surrounding this tract were acutely inflamed and edematous and showed numerous hemorrhagic points. The gastrointestinal tract and associated organs were essentially negative. The spleen was enlarged and the pulp was soft and friable. The kidneys were swollen and showed numerous absolutely round hemorrhagic spots on the outer cortical surfaces. A few of these were also seen in the cortical zone on cut section. There were numerous submucosal hemorrhages in the kidney pelves. The whole posterior muscular wall of the bladder and the soft tissues surrounding the rectum and overlying the sacrum were edematous and hemorrhagic. They appeared to be almost necrotic. This process extended to some extent behind the sacrum. The outer zones of the adrenal cortices were grayish in color and apparently contained less fat than normal. The central nervous system was edematous, but otherwise not abnormal grossly.

*Case No 5769*, male, age 46, fatal case, was admitted on the probable fifth day of the disease with the chief complaints of headache and pain in the legs. On admission the important findings on physical examination were as follows: Temperature 40.3° C p r. Pulse 80. Respirations 32. Blood pressure 108 mm Hg systolic and 80 mm diastolic. Weight 114 pounds. The patient appeared older than his stated age, undernourished and mentally dull. A maculo-papular rash was present over the upper arms, back, and upper legs. The lesions blanched on pressure. The skin of the face was dusky. The pupils were small, the conjunctivae were not suffused. The tongue was moist. Harsh breath sounds and liquid sounding rhonchi were present over the left lower lobe. There was no cardiac enlargement to percussion. A questionable apical systolic murmur was present. The brachial arteries appeared thickened and tortuous, with visible pulsations.

*Admission laboratory data*: Hemoglobin 87 per cent ( $\text{CuSO}_4$ ), red blood cells not determined. Urine dark amber in color, cloudy, reaction acid, specific gravity 1.026, albumin 2+, many squamous epithelial cells, 6-8 white blood cells and an occasional granular cast were seen in the centrifuged sediment. The non-protein nitrogen was 40 mg per 100 c c. The urea clearance was 122 per cent of normal. The electrocardiogram was within normal limits.

*Hospital course* (chart 6) The patient became steadily more ill throughout the first hospital week. The rash increased until the eleventh day of the disease. With the increase in rash he became progressively more drowsy. On the eighth day several light red spots were noted on the palms. The cough continued but no sputum was obtained. He was incontinent of urine. On the ninth day he vomited once and refused fluids. He was semistuporous and apparently quite deaf. On the tenth day he was stuporous but could be roused. He refused all fluids by mouth. The con-

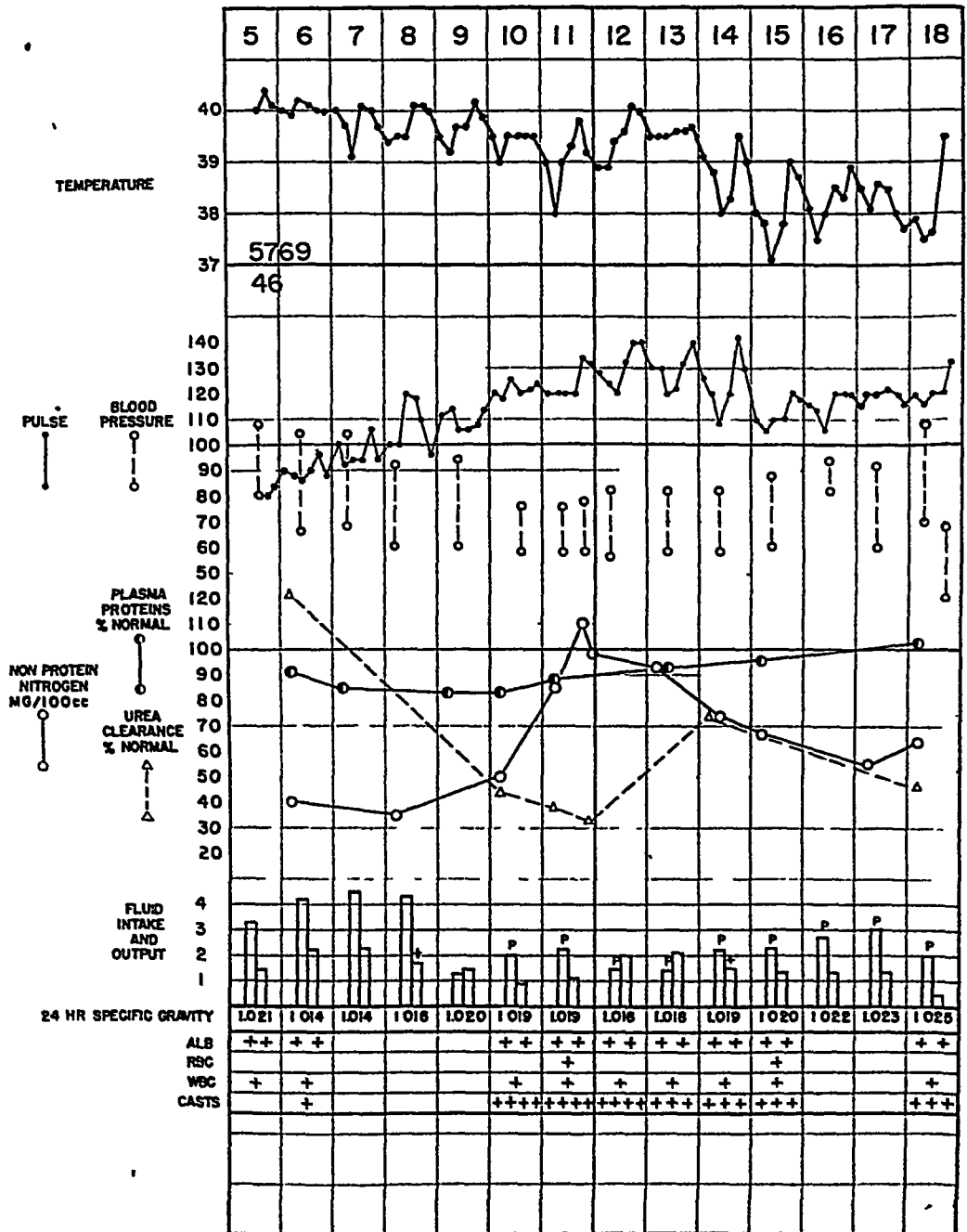


CHART 6 Case No 5769

junctivae were suffused. The tongue appeared to be slightly dry. The skin of the face was quite dusky. There were no changes in the chest signs from the findings on admission. The abdomen and extremities were negative. He was given 2000 cc of 5 per cent dextrose in saline subcutaneously. On the eleventh day the stupor had increased. The respirations were between 40 and 52 per minute throughout the day. The oral mucous membranes did not appear dry. The neck was slightly resistant to flexion. There were loud rhonchi and harsh breath sounds at the lung bases. The heart rate was rapid, the rhythm regular, and radial pulses were full. The abdomen, extremities, and reflexes were not remarkable. The rash became very profuse, and in some areas the macules were confluent. A dull erythema was present over the trunk. Two thousand cc of 5 per cent dextrose in saline were given subcutaneously. The outlook at this time was very poor.

On the morning of the twelfth day he appeared to be slightly improved. He was extremely drowsy and refused all fluids. A loose cough was present, but no sputum could be obtained. The skin of the face was still very dusky. The tongue showed a light brown coat but appeared moist. There was dullness to percussion and moist sounding râles were heard at the right lung base. The heart showed no changes from the previous day. There were no tremors. The reflexes were not hyperactive. The rash continued to be brilliant. The macules were both large and small and blanched on pressure. He was given 1,000 cc of 5 per cent dextrose in normal saline subcutaneously.

On the thirteenth day his general condition remained the same. The rash, however, appeared to be less florid. He was stuporous and completely disoriented. Parenteral fluid administration (2,000 cc) was continued daily until the day of death because of reluctance to take fluid by mouth.

On the morning of the fourteenth day he became quite talkative although still completely disoriented. However, restraints were not necessary. A loose, nonproductive cough was still present. The tongue and mucous membranes of the mouth appeared to be quite dry. The signs of congestion at the right lung base were less. The rash was still florid. It was noted that subcutaneous injections of 5 per cent dextrose in saline were being very slowly absorbed.

On the fifteenth day slight general improvement was noted. He was able to answer questions and breathe on request. The rash was fading.

General improvement appeared to continue on the sixteenth day. He had short periods of comparative mental clarity. His stupor was less evident. A loose cough was still present with no expectoration. Rhonchi and a few coarse râles were present over both lung fields. There was no dullness on percussion. The rash was still fading.

He appeared more stuporous on the seventeenth day, however, and the respirations had increased to over 50 per minute. He was not orthopneic. There was no increase in the area of precordial dullness. The heart sounds were loud, the action regular, and no murmurs were heard. The abdomen and extremities were negative.

On the eighteenth day of disease, however, his condition became critical. The respirations were increased to 50-60 per minute, there were audible tracheal râles, and no cough. He became profoundly stuporous. Harsh breath sounds were present over the upper lung fields with coarse râles over the left upper lobe and right and left lower lobes. There was no evidence of fluid. There was no change in heart size. The rhythm was regular. The abdomen was soft. No organs were palpable. The extremities showed no edema. The rash continued to fade. Postural drainage produced a large quantity of thin, yellow sputum. On smear this contained large numbers of polymorphonuclear leukocytes and gram-positive organisms, lancet shaped diplococci predominating. The patient was started on a regimen of penicillin therapy, but he rapidly became comatose and died.

No postmortem examination was obtained.

*Case No 5133*, male, age 30, fatal case, was admitted on the fifth day of disease with the chief complaint of severe headache. On admission the important findings on physical examination were as follows: Temperature 40.3° C pr. Pulse 96. Respirations 30. Blood pressure 114 mm Hg systolic and 70 mm diastolic. Weight 120 pounds. The patient appeared acutely ill. A cough was present, productive of a small amount of white sputum. A diffuse maculo-papular rash was seen over the back, chest, arms, abdomen, and legs to the ankles. Several bright red macules were present on the right palm. All the lesions blanched on pressure. The conjunctivae appeared moderately suffused. The tongue was white coated and dry. Coarse rhonchi were heard over both lung fields. The heart size appeared normal to percussion. The rhythm was regular. No murmurs were heard. The spleen was felt to descend 3 cm below the costal margin. The edge was firm, sharp, and not tender.

*Admission laboratory data* Hemoglobin 102 per cent (Sahli), red blood cells 5,140,000, white blood cells 7,500 with 86 per cent polymorphonuclear cells. Urine amber in color, cloudy, reaction acid, specific gravity 1.022, albumin 2+, many squamous epithelial cells and 1-3 granular casts per low power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 34 mg per 100 cc. The plasma proteins were 7.2 gm per 100 cc. A roentgenogram of the chest showed prominent lung markings and areas of calcification in the right hilar region. The electrocardiogram showed T-waves of borderline amplitude in Lead I.

*Hospital course* (chart 7) The patient became progressively sicker during the sixth and seventh days of his disease and developed severe diarrhea for a period of about 16 hours. In spite of a good fluid intake his tongue remained dry, petechiae appeared on the buccal mucous membranes, and the rash became more profuse. On the evening of the seventh day against orders, he was given 3 grains of nembutal. He remained very stuporous throughout the eighth day. The abdomen became distended and hiccoughs developed. The electrocardiogram showed low voltage of the QRS complexes. He was given 1,900 cc of 5 per cent dextrose in saline subcutaneously, but developed suppression of urine.

On the ninth day he was more alert. The cough was less in evidence but his respirations had increased to 44 per minute, though they were not labored. He felt more comfortable in a 45° sitting position. The face was exceedingly dusky, and the conjunctivae were injected. The tongue appeared slightly dry. Coarse rhonchi, but no dullness or râles, were heard throughout the lower lung fields. The heart rate had increased. The abdomen remained distended, no organs were felt. There was no peripheral edema. The rash remained profuse. By 7:00 p.m. he had not voided for nearly 36 hours, 440 cc of turbid urine was obtained by catheterization. A roentgenogram of the chest revealed small round shadows throughout both lung fields.

On the tenth day the patient's condition appeared worse. Mentally he was alert. Respirations remained elevated, but not labored. An occasional cough produced small amounts of tenacious white sputum. Periodic hiccoughs were still present. The face was darkly flushed. Intense conjunctival injection persisted. The rash remained profuse. There was no distention of the neck veins in the horizontal position. The hands and feet were warm. There was slight dullness over both lung bases, with inspiratory râles and expiratory rhonchi over both lower lobes. The area of cardiac dullness was not increased. The heart sounds were obscured by breath sounds. There were occasional involuntary twitches of the hands and fingers. Fluid intake by mouth had practically ceased. The electrocardiogram showed only T-waves of low amplitude in Leads I and II. He was put on continuous bladder drainage, and given a slow infusion of 2,000 cc of 5 per cent dextrose in saline.

On the eleventh day he became mentally confused. The respirations remained rapid. The chest signs appeared to be the same as on the previous day. The heart rate had increased. There were no signs of peripheral venous congestion. The abdomen was no longer distended. The sputum was purulent, containing many gram-

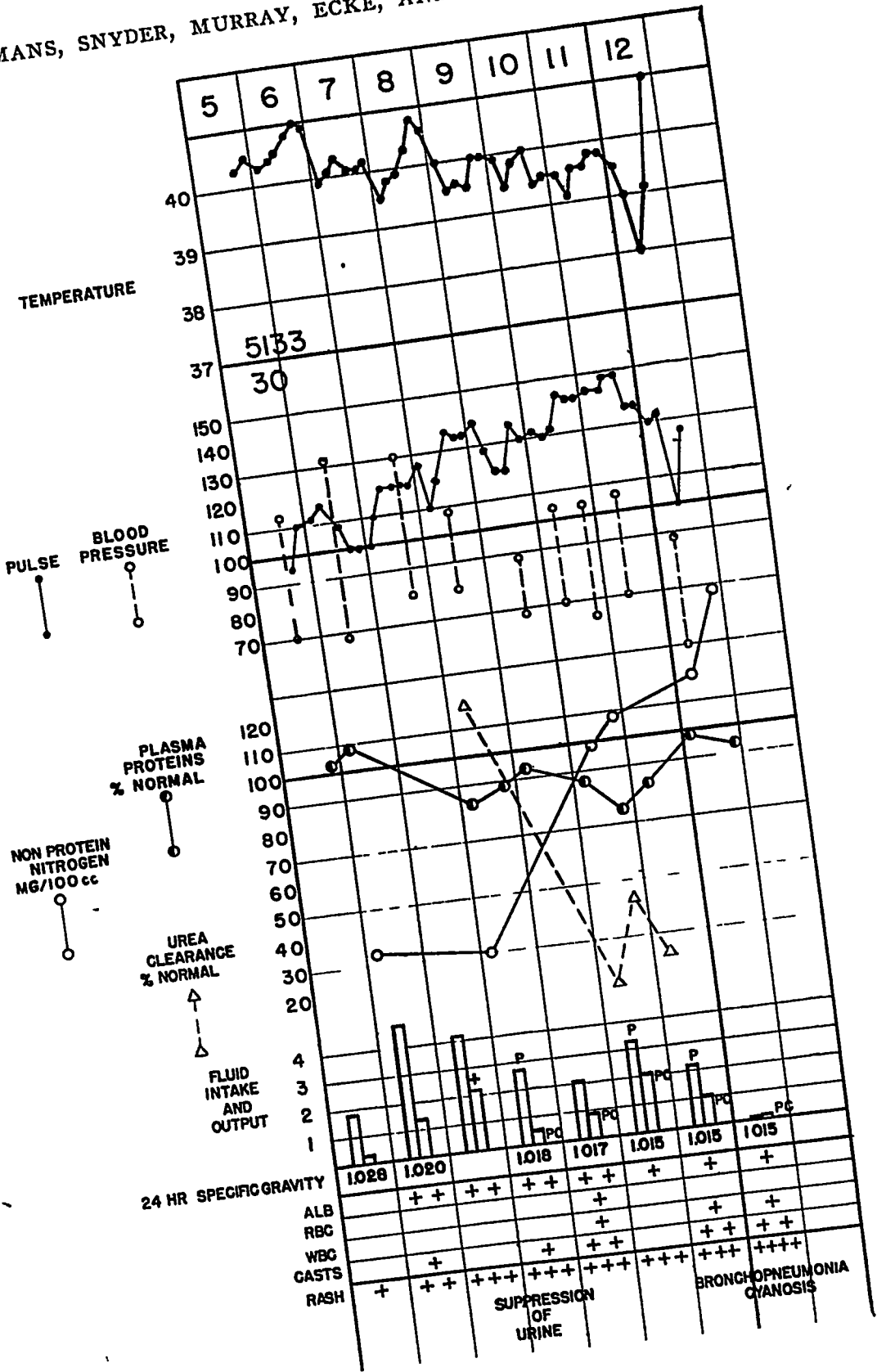


CHART 7 Case No 5133

positive organisms Intake by mouth was still much reduced He was given penicillin, 40,000 units intramuscularly every three hours, 400 cc of dextrose in saline intravenously, and 600 cc intramuscularly

On the twelfth day his condition became much worse He grew stuporous Audible tracheal râles appeared His lips and nail beds became cyanotic, his hands and feet grew cold The rash had become more profuse The blood pressure fell to 80 mm Hg systolic and 50 mm diastolic Crepitant râles appeared over both lower lobes posteriorly with a small area of bronchial breathing at the right base The heart sounds could not be heard nor the heart borders percussed The electrocardiogram showed T-waves of low amplitude in Lead I and of borderline amplitude in Lead II, and borderline low voltage of the QRS complexes He was given oxygen by face mask, intravenous caffeine with sodium benzoate, and 0.001 gm of strophanthin "G" The cyanosis was reduced somewhat by the administration of oxygen and the respiratory rate became less However, the blood pressure continued to remain low and at times the radial pulses were not felt When the face mask was removed for a few moments the cyanosis rapidly increased and the respirations became slow and gasping Towards evening the temperature mounted rapidly, respirations grew slower and ceased

At postmortem examination the rash was still present The pleural cavities contained no fluid The lungs were well aerated, except for an area of firm tissue the size of a walnut in the right lower lobe, and small areas in the dependent portions of both lower lobes, which on section appeared red and from which reddish fluid and pus could be expressed The heart weighed 320 gm and was contracted The pericardial and endocardial surfaces appeared normal The ventricular walls were of normal thickness The valves appeared normal The liver weighed 1,800 gm On section, the individual lobules were distinct The spleen (not weighed) appeared slightly enlarged The capsule was wrinkled, and on section the pulp appeared firm The kidneys appeared normal in size There were small hemorrhages in both renal pelves There were several small areas of submucosal hemorrhage in the wall of the bladder The brain weighed 1,200 gm The convolutions of both hemispheres appeared shrunken There was no evidence of edema The remainder of the post-mortem examination was grossly not remarkable

*Case No 7250*, male, age 30, fatal case, was admitted in the fourth day of the disease with the chief complaint of headache On admission physical examination the important findings were as follows Temperature 40.0° C pr Pulse 88 Respirations 36 Blood pressure 118 mm Hg systolic and 64 mm diastolic Weight 116 pounds The patient appeared moderately ill, mentally clear, with rapid respirations, and no cough A few poorly defined maculo-papular lesions were noted over the chest, abdomen and arms The conjunctivae appeared moderately injected The tongue was moist A few crepitant râles were heard on the right mid lung field posteriorly Examination of the heart was not remarkable The spleen was enlarged but not tender Its tip was felt 7 cm below the costal margin The liver was not palpable, but enlarged 3 cm below the costal margin by percussion

*Admission laboratory data* Hemoglobin 72 per cent ( $\text{CuSO}_4$ ), red blood cells 4,110,000, white blood cells 4,300 with 76 per cent polymorphonuclear cells Urine amber in color, reaction acid, specific gravity 1.023, albumin 2+, 8-10 white cells per high power field, and an occasional granular cast were seen in the centrifuged sediment The blood non-protein nitrogen was 30 mg per 100 cc The plasma proteins were 65 gm per 100 cc

*Hospital course* (chart 8) In spite of frequent sponging the patient continued to run a high fever from the fourth to the ninth day of disease On the fifth day the maculo-papular rash increased but the macules were still scanty and poorly defined On the sixth day the patient became disoriented On the eighth day he was quite drowsy and vomited twice His general condition, however, appeared satisfactory



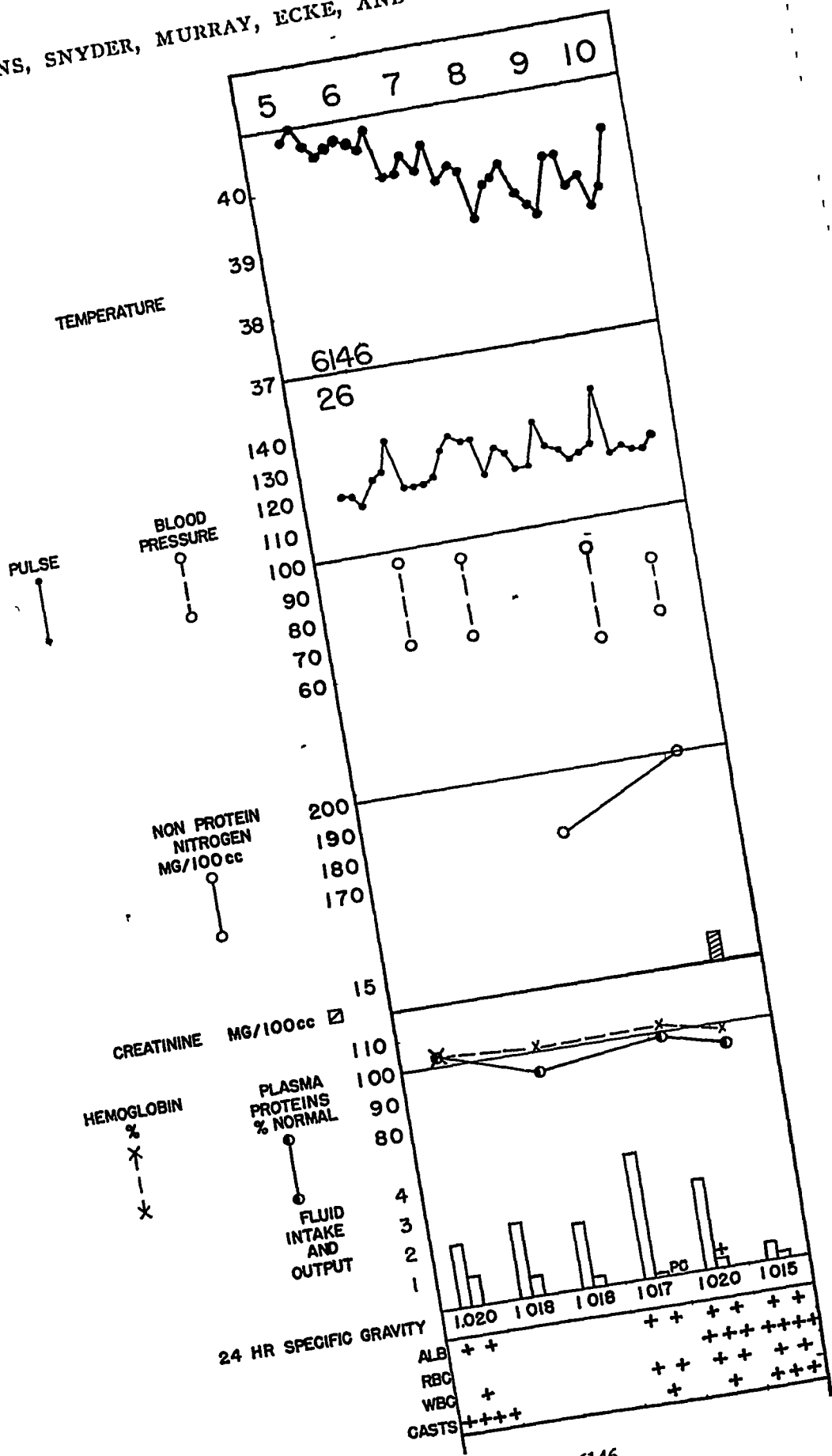


CHART 9 Case No 6146

rhythm was regular, and no murmurs were present. A hard, non-tender spleen was felt 3 cm below the left costal margin.

*Admission laboratory data* Hemoglobin 103 per cent ( $\text{CuSO}_4$ ), red blood cells 5,450,000, white blood cells 8,450 with 88 per cent polymorphonuclear cells. Urine light amber in color, cloudy, specific gravity 1.018, albumin 2+, a few squamous epithelial cells, many granular casts, 4-6 white blood cells per low power field were seen in the centrifuged sediment. The plasma proteins were 6.8 gm per 100 cc. A roentgenogram of the chest showed prominent hilar shadows and small dense shadows at the left lung base which suggested areas of calcification.

*Hospital course* (chart 9) The patient vomited several times on the seventh day, and the nonproductive, hacking cough continued until the ninth day. A few more light red macules made their appearance on the trunk. There were no changes in the chest signs from the time of admission examination. On the eighth day he was unable to void. He was given 2,000 cc of normal saline subcutaneously, and catheterized. His condition appeared worse on the ninth day. He was slightly disoriented, had coarse tremors of the upper extremities, and picked at his bedclothes. The rash became widespread and profuse, the conjunctivae intensely injected. The tongue and mucous membranes of the mouth and throat appeared to be very dry. Examination of the lung fields showed fine crepitations over both bases. The heart sounds were not well heard.

On the morning of the tenth day he became semicomatose. The cough ceased. He developed Cheyne-Stokes respirations. The conjunctival injection increased and the rash became more profuse. A brown, dry coat appeared on the tongue. Numerous petechial hemorrhages were seen on the buccal mucous membranes. The neck was not stiff. Signs in the chest were similar to those observed on the previous day. There was marked twitching of the hands, arms, and occasionally the legs. At noon the hands and feet became cold, the lips and nail beds cyanotic. Shortly thereafter he developed a Jacksonian convulsion and died.

At postmortem examination one hour after death the following findings were of interest. An extensive rash covered the entire body except for the face and neck, palms of the hands, lower legs and feet. The pleural cavities contained no free fluid. There was a small area of firm tissue at the base of the left lung which appeared red and dry on cut section. The bronchi contained a moderate amount of viscid yellowish exudate. The mucosa of the large bronchi was intensely reddened. The heart appeared of normal size with no gross abnormalities. The spleen was of normal size, and on cut section the pulp was firm. The kidneys appeared to be of normal size, and the surfaces were smooth. Minute dark red circular spots were found on the surface of both kidneys, but on cut section there were no gross abnormalities to be seen. Small areas of hemorrhage were seen in both renal pelves and on the mucosal surface of the bladder. The left adrenal gland appeared normal. The right was not examined. The brain appeared grossly normal. The remainder of the gross examination was not remarkable.

*Case No 7464*, male, age 43, fatal case, was admitted on the sixth day of disease with the chief complaints of headache and generalized aches and pains. On physical examination the important findings were as follows: Temperature  $39.8^\circ\text{C}$  p r. Pulse 100. Respirations 40. Blood pressure 100 mm Hg systolic and 60 mm diastolic. Weight 129 pounds. The patient's general condition appeared good, he was mentally clear and objectively deaf. There was a light erythema over the back and a few suspicious appearing spots on the anterior thighs and about the hips which suggested an early typhus rash. The conjunctivae were suffused. The tongue was moist. Coarse rhonchi were heard over the lung fields. The heart size appeared normal to percussion. The action was regular, and there were no murmurs. The spleen was enlarged 3 cm below the left costal margin. The edge was sharp and not tender.

*Admission laboratory data* Hemoglobin 85 per cent ( $\text{CuSO}_4$ ); red blood cells 4,020,000, white blood cells 2,550 with 81 per cent polymorphonuclear cells. Urine amber in color, cloudy, reaction acid, specific gravity 1.010, albumin 1+, many squamous epithelial cells, 1-3 white blood cells and an occasional red blood cell per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 25 mg per 100 c.c. The urea clearance was 118 per cent of normal. The plasma proteins were 5.1 gm per 100 c.c. A roentgenogram of the chest showed a generalized increase in the lung markings but otherwise appeared negative.

*Hospital course* (chart 10). During the sixth, seventh, and eighth days of disease the patient had a high fever requiring almost constant sponging to keep the temperature below  $40.5^\circ \text{C}$ . The rash became increasingly evident and the patient more drowsy.

On the ninth day slight delirium was present. The tongue and oral mucous membranes appeared slightly dry, and fine inspiratory râles were heard over both lower lung fields, but no signs of consolidation could be elicited. The sputum was yellow, blood streaked, tenacious, and contained many gram-positive organisms.

On the tenth and eleventh days the patient became progressively more stuporous, chest signs continued, but no evidences of consolidation were present. The white blood cell count on the tenth day was 11,050 with 78 per cent polymorphonuclear cells. Muscular twitching of the face was noted. On the eleventh day the rash was definite and widespread over the trunk.

On the morning of the twelfth day he was semicomatose and cyanotic. Signs of consolidation appeared over the right lower lung field. A roentgenogram of the chest showed a high right diaphragm with numerous soft shadows in the right lower lung field. An electrocardiogram showed low voltage with frequent ventricular extrasystoles. The patient was given 300 c.c. of plasma intravenously and 300 c.c. of 5 per cent dextrose in saline, and oxygen by face mask. Penicillin therapy was begun with an initial dose of 50,000 units intravenously followed by 40,000 units intramuscularly every three hours thereafter. His general condition appeared to improve. The blood pressure did not fall, and the heart rate remained about 110 beats per minute. In the evening definite pitting edema of the lower arms and feet was present.

On the morning of the thirteenth day the blood pressure had dropped to 84 mm Hg systolic and 48 mm diastolic. The patient was comatose, and respirations were rapid and shallow. There were no changes in the lung signs from the previous day. The extremities were warm. The patient was given 600 c.c. of plasma intravenously, and rapid digitalization was begun. The blood pressure rose throughout the day to 110 mm Hg systolic and 48 mm diastolic in the afternoon. The electrocardiogram continued to show low voltage with T-waves of low amplitude in Leads I and II. Ventricular extrasystoles were no longer present. Cyanosis of the lips and nail beds continued. When the oxygen mask was removed for a few moments the radial pulses became weak and the cyanosis increased. The edema appeared to decrease slightly throughout the day. Aside from occasional twitching of the fingers no abnormal neurological signs were noted. In the early evening respirations became intermittent and ceased.

At postmortem examination important findings were the following. The rash was still present. The left ventricle was contracted. The cut surface of the myocardium was brownish in color. The dependent portions of the right and left lower lobes of the lungs were firm, dark red, and exuded thick yellowish exudate on pressure. The bronchial mucosa was intensely reddened. The spleen was enlarged to about twice its normal size and was soft in consistency. The right and left kidneys weighed 210 and 180 gm, respectively. Pin-point hemorrhagic spots were present on their surfaces and petechial hemorrhages were seen in the renal pelves. The brain appeared grossly normal.

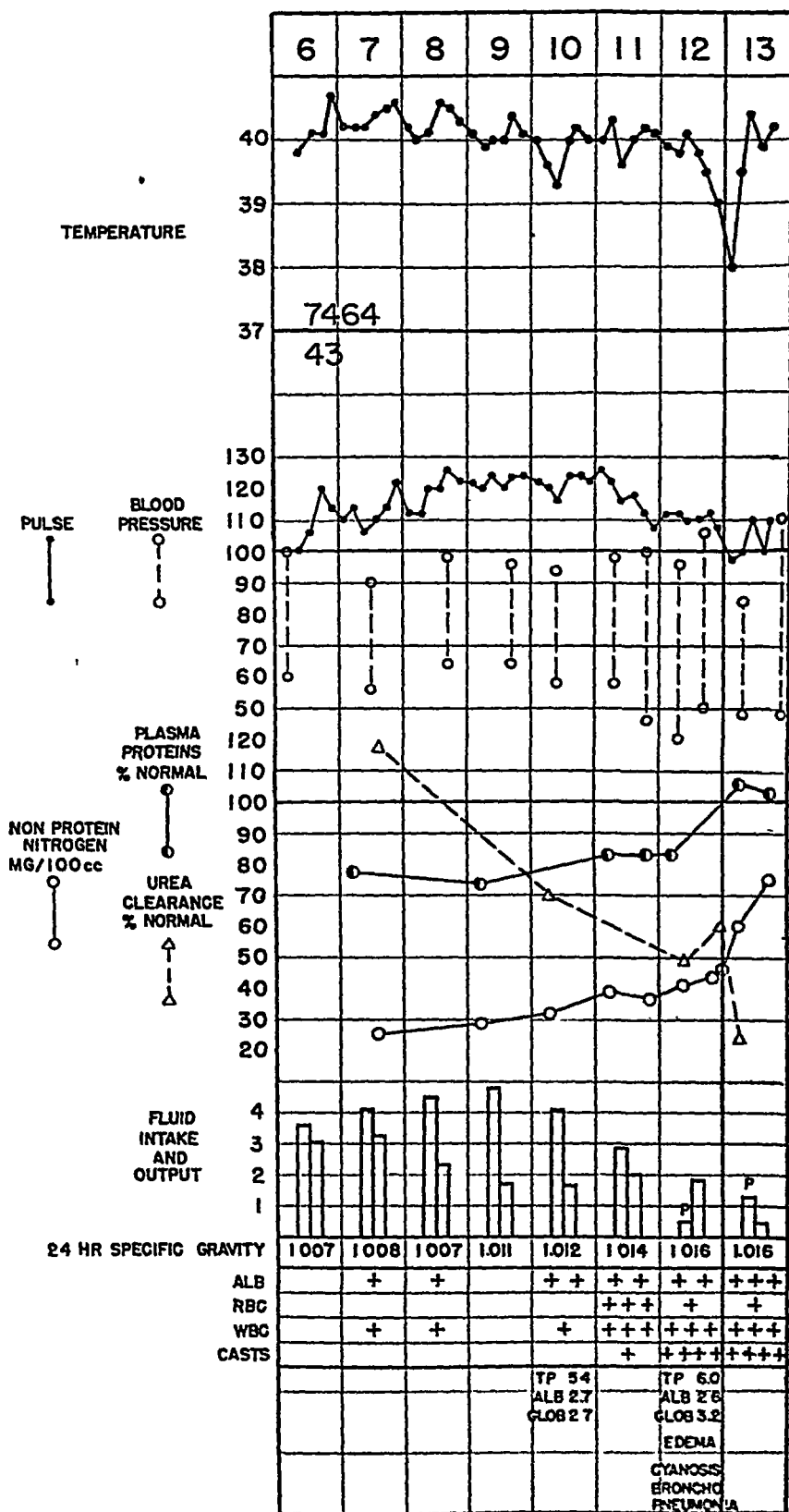


CHART 10 Case No 7464

## COMMENT

The data presented show that abnormal concentrations of blood non-protein nitrogen occurred in a high percentage of typhus patients during the febrile course of the disease. Azotemia was particularly frequent in the critically ill patients and a universal finding in fatal cases.

Additional information is needed to determine all the possible factors which may be responsible for the development of this condition in typhus. The observations obtained from this group of 64 cases, however, allow one to consider certain important phenomena which are present in this disease and appear to be associated with the development of nitrogen retention.

Since it is known that the greatest portion of the blood non-protein nitrogen is eliminated by way of the kidneys, the level of the blood non-protein nitrogen will rise when the formation of nitrogenous metabolites proceeds at a more rapid rate than the elimination of these metabolites in the urine. In certain febrile states associated with a great increase in protein catabolism the excretion of excessive amounts of non-protein nitrogen is dependent upon the existence of a urine volume sufficient for this purpose. When the volume of urine is reduced in the presence of one or more factors such as dehydration, or lowered arterial pressure, or when intrinsic renal damage is present with or without these factors, the excretion of non-protein nitrogen may be delayed to the point where abnormal concentrations are found in the blood.

The fundamental injury to the body in typhus is the widespread invasion of the endothelial cells of the blood vessels by rickettsiae. Thromboses of varying degree may follow such invasion and result in anoxemia and death of tissue cells. It appears certain that in the moderately or severely ill typhus patient considerable destruction of body protein takes place, particularly since the protein and caloric intake of the diet are almost always grossly insufficient. An increase in protein destruction under these conditions may be reflected in increased amounts of non-protein nitrogen in the urine.

Nitrogen balance studies were not done in this series of patients. The diet for the majority of patients during the acute phase of the disease consisted of water, sweetened fruit juice, and 600-1000 c c of whole milk per 24 hours. For example, during the first 16, 15, and 19 days of hospitalization patients No. 4690, 5508 and 5808 respectively, remained on this diet. It may be stated, therefore, that the intake of protein in these three cases, as well as in others, was far below that which is considered the minimum for normal individuals. Likewise, the total daily caloric intake was much lower than desirable.

A loss of weight between 15 and 30 pounds was the rule in severely ill patients during the febrile period of the disease. The patients observed were from the lowest social strata of the population. They were almost without exception lean men, with no excess fat when in good health. Under

these conditions it is probable that the great loss in weight which they experienced was due in most instances to the loss in body proteins

Evidence obtained from the urea nitrogen values in urea clearance tests indicates that very large amounts of urea nitrogen alone must have been excreted by the kidney during the acute period of illness (table 6). In patient No 5808, for example, large amounts of urea nitrogen were found in the urine on the fifteenth and nineteenth days of disease when the total caloric intake was almost entirely confined to parenteral 5 per cent dextrose in saline

TABLE VI

The Estimated 24 Hour Output of Urine Urea Nitrogen in Typhus Fever, Based on Urine Urea Nitrogen Values Obtained during 2 Hour Urea Clearance Tests and Total Output of Urine during the 24 Hour Period

| Case No | Day of Disease | Blood Urea Nitrogen | Urine Urea Nitrogen | Estimated 24 Hour Output of Urea Nitrogen |
|---------|----------------|---------------------|---------------------|---|
|         |                | mg /100 c c         | gm /liter           | gm  |
| 4690    | 12             | 27                  | 6 2                 | 7   |
|         | 14             | 57                  | 8 1                 | 9   |
|         | 19             | 15                  | 10 0                | 11  |
| 5508    | 5              | 22                  | 11 2                | 17  |
|         | 7              | 17                  | 6 7                 | 15  |
|         | 10             | 23                  | 6 8                 | 19  |
|         | 14             | 20                  | 6 1                 | 16  |
|         | 17             | 20                  | 7 2                 | 24  |
| 5808    | 15             | 33                  | 14 2                | 16  |
|         | 19             | 16                  | 7 7                 | 12  |
|         | 35             | 13                  | 6 7                 | 13  |

Likewise, the estimated output of urea nitrogen in patient No 5508 suggests that the excretion of total nitrogen must have been considerable, particularly in view of the very low protein intake (table 6). Although a loss of 21 pounds occurred in the first 14 days under observation in this case, nitrogen retention was minimal. This case illustrates the ability of some typhus patients to excrete large amounts of non-protein nitrogen with practically no rise in the blood urea nitrogen when the urine volume is above 2,000 c c daily.

As we have stated in the presentation of the data, azotemia appears to be closely associated with a decreased output of urine in cases which demonstrate efficient concentrating power of the kidneys by excreting urine with high specific gravities. The data on patient No 5808 are illustrative. On the twelfth and thirteenth days of disease the fluid intake had decreased to little more than 1,000 c c in 24 hours. There was a simultaneous increase in urine concentration above 1 020. The blood non-protein nitrogen had not risen over 50 mg per 100 c c after 48 hours of greatly reduced fluid intake in the presence of high fever. From the thirteenth to the eighteenth day of disease the fluid intake was almost entirely parenteral, the daily volume was small in amount. In the presence of a rising urine specific gravity there oc-

curred a rapid rise in blood non-protein nitrogen concentration. The urea clearance at that time was within normal limits. There then followed a decrease in blood urea nitrogen concentration with the decline in temperature to normal. The daily urine volumes, however, were still low and the specific gravities were high. This case illustrates the important probability that in the presence of good renal function a low output of urine may be responsible for azotemia in typhus. In such situations it appears that the low urine volume delays the excretion of excessive amounts of non-protein nitrogen with the result that high concentrations are found in the blood.

In contrast to the phenomena observed in patient No. 5808, there were other cases in which the daily urine volumes rarely exceeded 1500 c.c., but the specific gravities and urea clearances indicated a definite diminution in renal function. The data on cases No. 3307, 4690, 5133, 5769, and 7250 show that azotemia in these patients was associated with one important phenomenon which we have as yet not sufficiently considered. This was a rapid fall in arterial blood pressure.

Changes in renal function associated with changes in peripheral blood pressure<sup>37</sup> lead one to believe that significant changes in renal blood flow affecting renal function<sup>38</sup> might have been demonstrated in some or all of these cases if the newer methods<sup>38</sup> for the study of renal physiology in man had been utilized.

From the data on the five patients noted above the obvious phenomena associated with the presence or development of a low peripheral blood pressure were a decrease in the urine volume, urea clearance, and rise in the blood non-protein nitrogen. When observed, the fall in blood pressure occurred in the space of a few hours. It was of varying duration.

Another finding of importance which was common to these cases was the development of a urine specific gravity low in relation to the daily urine output. A state of renal insufficiency developed in these patients following the sudden fall in arterial pressure. This was characterized by a diminution in urine volume, a loss in concentrating power of varying degree, with a fall in urea clearance. The data indicate that the renal failure observed was at least initiated by extrarenal factors.

Although of serious prognostic import, this type of renal failure was not always progressive, even in cases which terminated fatally. Cases No. 3307 and 5769 showed a tendency for renal function to improve in the final days of life. In most cases renal failure did not improve and was associated with rapid death, as exemplified by cases No. 5133, 6146, and 7250.

A few patients who developed this type of renal failure recovered from typhus. The sequence of events outlined on the chart of patient No. 4690 was quite characteristic for this small group. With the rise in blood pressure there was an associated return of renal function with a fall in the blood non-protein nitrogen. The supportive treatment of such cases did not differ in any way from that employed in cases which developed renal insufficiency and later died.

Although the majority of fatal cases appeared to develop renal insufficiency preceded by a rapid fall in blood pressure, there were rare cases observed in which this factor was not seen. The data on patient No 7464, for example, suggest that renal insufficiency developed several days before death in the absence of a fall in blood pressure or increasing dehydration. It cannot be denied, however, that the blood pressure during hospitalization in this patient may have been much lower than before he came under observation. It may be, nevertheless, that an overwhelming rickettsial infection, such as this patient demonstrated clinically, affects renal function through mechanisms which are at present unrecognized. The possible direct effect of rickettsial toxic substances upon the kidney, for example, is unknown.

A discussion of the possible causes for the rapid fall in arterial pressure is beyond the scope of this paper. Recent studies have been made concerning alterations in the cardiovascular system in typhus<sup>2, 15, 16, 17</sup>. Our studies of the cardiovascular changes associated with this disease are still in progress and will be reported in a later communication.

One of our cases merits special attention since the course of events in this man's illness was unique in our experience with typhus. Patient No 1109, an "E" case, showed evidences of severe renal insufficiency throughout his hospital course. The urine specific gravity remained relatively fixed in spite of large fluctuations in the daily output. Increasing dehydration was neither in evidence clinically nor by observation of the plasma protein levels. After the first hospital day his diastolic blood pressure remained consistently elevated for 16 days. He developed an anemia of far greater severity than is usually seen in typhus, together with edema and hypoproteinemia. Serial electrocardiograms showed evidence of extensive myocardial changes. Numerous red cells and red cell casts appeared in the urine during the fourth week of his illness. His convalescence was complicated by otitis media and erysipelas. Follow-up examinations over a nine month period showed consistently diminished concentrating power of his kidneys with albuminuria, occasional red cells, white cells, granular and hyaline casts. His basal diastolic blood pressure was elevated at times to 90 mm of mercury. The red blood cell count returned to normal but the electrocardiograms remained persistently abnormal.

The diastolic blood pressure levels present during the acute phase of this patient's disease have so far not been observed by us in any other severe case of typhus. A diastolic level of between 86 mm and 90 mm of mercury in severe typhus constitutes a relative hypertension which is not without significance. The specific gravity of the 24 hour urine samples, furthermore, suggests that the degree of nitrogen retention found was dependent upon renal failure rather than on deficient fluid intake in the presence of good renal function. The phenomena observed in this case may be explained either by assuming that this patient had considerable hypertension before



the onset of typhus, with a relatively severe drop in blood pressure during the disease,—a theory not upheld by subsequent studies in this case since the blood pressure was not found greatly elevated at any time during the follow-up examinations—or that the course of typhus fever was associated with an acute nephritis. In this regard one may speculate whether or not latent nephritis was present before the onset of typhus. No history of previous headaches, edema, or abnormal appearance of the urine was obtainable. However, there was evidence in the form of persistent albuminuria and diminution in the concentrating power of the kidneys to confirm the belief that residual renal damage was still present. In view of our experience to date that severe renal insufficiency in typhus is closely associated with extrarenal factors and has never yet been shown conclusively to produce persistent renal damage in cases which recover, we believe this patient most probably had chronic renal disease with an acute exacerbation during the course of typhus. The electrocardiographic changes which persisted for almost a year after the disease are unique in our experience, and indicate that extensive involvement of the heart was present during the acute phase of typhus resulting in permanent myocardial changes.

In concluding the comment on the data presented we can state that our studies have so far indicated that the development of nitrogen retention in this disease is the result of a number of factors which may be more often encountered in typhus than in other acute infectious diseases.

To begin with, the circumstances under which epidemic louse-borne typhus occurs and is observed impose a fundamental consideration in the concept of the origin of azotemia in this disease, namely, that the caloric and protein intake of nearly all typhus patients is grossly insufficient. There is good reason to believe that the destruction of the body tissues must be considerable. As a result of such tissue destruction, the elimination of large amounts of non-protein nitrogen is dependent upon a larger daily volume of urine than would otherwise be necessary if protein catabolism were proceeding at a more normal rate. In order to prevent the accumulation of nitrogenous metabolites in the blood, the excretion of an adequate output of urine for this purpose is necessary. In the presence of greatly increased protein catabolism it is apparent that dehydration with a diminished output of urine will have considerable effect upon the degree of azotemia observed.

Another factor closely associated with the development of azotemia in typhus is encountered in the more critically ill patients and is of the greatest importance. This is the onset of renal insufficiency, most often associated with a rapid fall in blood pressure. The renal insufficiency met with in these patients is of serious prognostic import. In our experience the patients who have survived have been very few in number. We do not imply that the cause of death in such cases is renal failure. The majority of these patients died with evidences of overwhelming rickettsial infection or complicating conditions such as pneumonia. Nevertheless, a rapid diminution in kidney

function was almost without exception the first indication that the patient would probably succumb to the disease. The presence of renal insufficiency itself was of more significance than a fall in blood pressure, since at times such a fall was not observed or occurred in the absence of renal failure. At present we have no evidence to indicate that the loss of renal function observed in these critically ill patients was due to other than extrarenal factors.

In addition to deficient total caloric intake and tissue protein destruction, dehydration, and the rapid development of renal insufficiency in typhus, there may be other factors which are important in the production of azotemia in this disease. As yet we lack important data on the type of circulatory failure which may be present in some patients, as well as alterations in electrolyte balance, renal blood flow, and pathologic histologic changes in the kidney, which may be found in cases similar to those cited in this paper. Obviously, much additional information is needed before all the phenomena which may contribute to the development of azotemia in typhus are well understood.

### SUMMARY AND CONCLUSIONS

The experience with "untreated," unvaccinated typhus fever patients during two epidemic years has been analyzed with reference to the incidence of nitrogen retention and to certain factors which may contribute to its development. The data were obtained from 64 patients on the United States of America Typhus Commission ward and 14 patients on the general wards of the Cairo Fever Hospital.

Azotemia in epidemic louse-borne typhus fever was found to occur very frequently (in 52 per cent of the cases), as indicated by elevated concentrations of blood non-protein nitrogen, urea nitrogen, and creatinine.

The correlation between clinical severity and azotemia was striking. Elevated concentrations of blood non-protein nitrogen were found in every fatal case whose blood was examined.

This phenomenon was not restricted to older age groups. With one exception positive evidence for glomerular nephritis was lacking in all cases in which the urine was frequently examined. Follow-up examinations over a period of months have shown no impairment of renal function in even the most critically ill patients with severe renal insufficiency, except in rare instances in which the possibility exists that renal disease was present before the onset of typhus.

In this series of typhus cases azotemia appeared to be closely associated with excessive destruction of body protein and increased nitrogen excretion, with dehydration and a reduced output of urine in the presence of normal kidney function, and in severe cases with a sudden rapid fall in blood pressure associated with evidences of renal insufficiency.

The appearance of renal insufficiency as a complicating condition in the disease was in nearly every instance the earliest indication that the patient's course would be very severe or would end fatally.

## ACKNOWLEDGMENTS

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## BIBLIOGRAPHY

- 1 PETERS, J. P., and VAN SLYKE, D. D. Quantitative clinical chemistry, 1935, Williams and Wilkins, Baltimore, 1, 266
- 2 WOODWARD, T. E., and BLAND, E. F. Clinical observations in typhus fever with special reference to the cardiovascular system, *Jr Am Med Assoc*, 1944, cxxvi, 287-293
- 3 WOLBACH, S. B. Typhus fever, in *Cecil's Textbook of Medicine*, Ed 4, 1937, W. B. Saunders, Philadelphia, pp 86-95
- 4 GORDON, J. E. Virus and rickettsial diseases, *Harvard School of Public Health Symposium*, 1940, Harvard University Press, Cambridge, pp 828-839
- 5 WOLBACH, S. B., TODD, J. L., and PALFREY, F. W. The etiology and pathology of typhus, 1922, Harvard University Press, Cambridge
- 6 DYER, R. E. The rickettsial diseases, *Jr Am Med Assoc*, 1944, cxxiv, 1165-1172
- 7 MEGAW, J. W. D. Louse-borne typhus fever, *Brit Med Jr*, 1942, ii, 401-433
- 8 KAMAL, A. M., and MESSIH, G. A. Typhus fever (review of 11,410 cases) symptomatology, laboratory investigations, and treatment, *Jr Egyptian Pub Health Assoc*, December 1943, 125-213
- 9 MURCHISON, C. Treatise on Continued Fevers of Great Britain, 1862, Parker, Son, and Bourn, London
- 10 WAGNER, F. Über das Verhalten des Reststickstoffes bei Infektionskrankheiten, *Wein Arch f inn Med*, 1920, i, 575-638
- 11 WALTHER, G. Das klinische Bild des Fleckfiebers, *München med Wchnschr*, 1942, lxxxix, 299-304
- 12 STURM, A. Das Fleckfieber und seine Bedeutung für die klinische Pathologie des Stammhirns, *Klin Wchnschr*, 1942, xxi, 899-904
- 13 WETZEL, U. Fleckfieber und Nierenschädigung, *Med Klin*, 1940, xxxvi, 1312-1313
- 14 ASCHENBRENNER, R. Über uramische Zustände beim Fleckfieber, *Klin Wchnschr*, 1944, xxiii, 8-12
- 15 ASCHENBRENNER, R. Die Herz- und Kreislaufstörungen beim Fleckfieber und ihre Behandlung, *Klin Wchnschr*, 1943, xxii, 1
- 16 HERZOG, E. Anatomia e histologia pathologica de las lesiones organicas de tifus exantematico durante la ultima epidemia en Chile (1932-35), *Reunion de la Soc Argentina de Path Reg del Norte*, 1935, ix, 574-600. Reviewed in *Centralbl f allg Path u path Anat*, 1937, lxxviii, 15
- 17 JULLIARD, J., and HENAFF, M. Troubles du metabolisme hydro-chlorure au cours des typhus epidemique et murin, *Rev du Serv de San Mil*, 1939, cx, 197-266
- 18 SEIDEX, H., KASPERCZIK, K., and FANTA, H. Kreislaufstörungen in der Fleckfiebergene-sungszeit, *Klin Wchnschr*, 1943, xxii, 179-182
- 19 ROBBERS, H. Cerebral bedingte Blutdrucksteigerung nach Fleckfieber, *Klin Wchnschr*, 1943, xxii, 116-119
- 20 RAETIG, H. Kombinierte Fleckfieberbehandlung mit Rekonvaleszenten Serum und Eigenblut, *Klin Wchnschr*, 1943, xxi, 560-563
- 21 BUHLER, F. Zur Behandlung des Fleckfiebers mit Rekonvaleszentenblut, *München med Wchnschr*, 1944, xci, 5
- 22 PFEFFER, G., and GAUWERKY, F. Gunstige Wirkung von Rekonvaleszentenblut auf den Verlauf des Fleckfiebers, *Klin Wchnschr*, 1943, xxii, 481-484.

- 23 LADTIN, K Erfahrungen bei Fleckfieber, Munchen med Wchnschr, 1943, xc, 1
- 24 SCHULTEN, H Das Fleckfieber bei Geimpften, Klin Wchnschr, 1944, xciii, 12-13
- 25 BRANDENBURGER, P Zur Behandlung des Fleckfiebers, Deutsch med. Wchnschr, 1944, lxx, 329-331
- 26 LAMPERT, H Eine neue Allgemeinbehandlung schwerer Infektionskrankheiten erläutert am Fleckfieber, Munchen med. Wchnschr, 1944, xci, 223
- 27 URRÁ, I A Fleckfieber in Spanien, Deutsch med. Wchnschr, 1944, lxx, 60-62
- 28 KORANYI, A, and VARGA, A Das Hepato-renal Syndrom bei Flecktyphus, Munchen med Wchnschr, 1943, xc, 582
- 29 BAYNE-JONES, S The United States of America Typhus Commission, Army Med Bull, July 1943, No 68, 4
- 30 Letter of Dr N H TOPPING, National Institute of Health, to the Director of the United States of America Typhus Commission, dated November 6, 1943
- 31 PLOTZ, H, WERTMAN, K, and BENNETT, B L The serological pattern in epidemic typhus fever 1 The development of complement-fixing antibodies, From the Division of Virus and Rickettsial Diseases, Army Medical School, Washington 12, D C, December 1943 To be published
- 32 Unpublished observations of the authors
- 33 YEOMANS, A, SNYDER, J C, and GILLIAM, A G The therapeutic effects of concentrated hyperimmune rabbit serum in louse-borne typhus fever, Jr Am Med Assoc., 1945, cxxix, 19-24
- 34 YEOMANS, A, SNYDER, J C, MURRAY, E S, ZARAFONETIS, C J D, and ECKE, R S The therapeutic effect of para-aminobenzoic acid in louse-borne typhus fever, Jr Am Med. Assoc., 1944, cxxvi, 349-356
- 35 ECKE, R S, GILLIAM, A G, SNYDER, J C, YEOMANS, A, ZARAFONETIS, C J D and MURRAY, E S The effect of Cox-type vaccine on louse-borne typhus fever To be published
- 36 VAN SLYKE, D D, RHOADES, C P, HILLER, A, and ALVING, A S The relationships between urea excretion, renal blood flow, renal oxygen consumption, and diuresis The mechanism of urea excretion, Am Jr Physiol, 1934, cix, 336-374
- 37 LASSEN, H C A, and HUSFELDT, E Kidney function and blood pressure, Jr Clin Invest., 1934, xiii, 263-278
- 38 GOLDRING, W, and CHASIS, H Hypertension and hypertensive disease, 1944, The Commonwealth Fund, New York

# OBSERVATIONS ON THE TREATMENT OF GRAVES' DISEASE WITH THIOURACIL\*

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OVER two years have elapsed since Astwood<sup>1</sup> first reported his observations on the use of thiouracil in a patient with thyrotoxicosis. It is now well known that the drug has a remarkable effect in preventing the formation of thyroid hormone and that its clinical use may cause striking improvement in the symptoms of Graves' disease. Unfortunately experience has also shown that the drug possesses some serious toxic properties and especially a tendency to cause granulocytopenia or even fatal agranulocytosis. It is not yet established whether it is safe for general use, whether under any circumstances its use constitutes a permanent cure or to what extent it may be regarded as a substitute for surgery. These are questions which can be answered only by extensive clinical trial. The drug is being widely studied, and numerous reports of its use have appeared in the recent literature.

Our experience with thiouracil at New York Hospital has accumulated since September 1943, and during the intervening 21 months a study has been made of 100 cases of hyperthyroidism. These included all thyrotoxic patients who were admitted to the medical wards during the period, three from the surgical service, five from the private practice of members of the staff, and two cases of mild Graves' disease who were treated ambulantly in the out-patient department.

Since patients entering the medical wards were taken without selection, the experience has been varied, and includes many of the vicissitudes which are likely to be encountered in the use of the drug. Some of the data concerning those who were treated are presented in table 1. Severe, mild and recurrent cases were included in the series. The majority of the goiters were classified as diffusely hyperplastic but there were many frankly nodular glands. The size varied greatly from several which could not be palpated by clinical examination to one huge, irregularly nodular goiter which compressed the veins of the neck and hung over the clavicles and sternum. Some of the patients had symptoms of very recent origin. One man had had the manifestations of Graves' disease for at least 25 years. Complicating conditions were numerous and included coronary and rheumatic heart disease, peripheral vascular disease, bronchiectasis, epilepsy, nephrolithiasis, and several psychoneuroses.

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## CIRCUMSTANCES OF THE STUDY

*Hospitalization* With two exceptions treatment during the intensive use of thiouracil was carried out in the hospital. Hospitalization was regarded as desirable because of the possibility of insidious development of toxicity, which might be recognizable only through close clinical observation and the prompt use of laboratory aids. It also served to make studies of clinical and chemical changes more inclusive than could be accomplished easily in the out-patient department. Several of the patients were intensively

TABLE I

|  |     |
|--|-----|
| Total Number of Cases Exposed to Thiouracil                                      | 100 |
| Time under Observation   |     |
| For 21 months  | 2   |
| over 18 months   | 13  |
| over 12 months   | 26  |
| over 6 months  | 29  |
| less than 2 months   | 8   |
| Age  |     |
| varied from 15 to 68 years   |     |
| Sex  |     |
| Women  | 80  |
| Men  | 20  |
| Duration of Illness  |     |
| 6 weeks to 25 years  |     |
| Severity of Disease  |     |
| B M R varied from +2 to +72  |     |
| Only 4 cases treated with initial B M R below +20                                |     |
| Previous Use of Iodine   |     |
| 19 patients were known to have received iodine up to time thiouracil was started |     |
| Previous Thyroidectomy   |     |
| 2 patients had had 3 operations  |     |
| 1 patient had had 2 operations   |     |
| 4 patients had had 1 operation   |     |
| Type of Goiter   |     |
| Series included both diffusely hyperplastic and nodular goiters                  |     |

studied in the metabolism ward of the Russell Sage Institute of Pathology. In those treated on the wards of the medical service a routine was established by which a variety of preliminary observations was obtained. The basal metabolic rate was determined before treatment often enough to establish a control level. The greatest circumference of the neck was recorded and careful exophthalmometric measurements were taken with the Hertl exophthalmometer. In addition to record of the pulse rate and blood pressure, the circulation rate was obtained by the use of decholin. Venous pressures were measured whenever the initial venous pressure appeared to be elevated. In many cases there were studies of cholesterol content of the serum, creatinine excretion, spontaneous creatinuria, and creatine tolerance. In a few cases sugar tolerance tests were made. Chemical tests for blood sugar, blood urea nitrogen, total protein, albumin-globulin ratio, calcium, phosphorus, and phosphatase in the serum were made routinely. All of these tests and measurements were repeated during or at the end of the intensive therapy before the patient was discharged from the hospital. In addition, white blood cell and differential counts were made at one to two day intervals.

In all but the earliest cases, icterus indices and prothrombin times were determined with the idea of detecting any possible hepatic damage

*Dosage of Thiouracil* The dosage of the drug varied In the earliest cases 0.8 gm was given daily in divided doses When beneficial effects were delayed, the dose was increased to 1.0 or to 1.2 gm and in one instance to 2.0 gm daily Later, and in the majority of cases here reported, 0.6 gm of thiouracil was given during the day in 6 doses of 0.1 gm each Such intensive therapy was continued until the basal metabolic rate had attained normal levels From review of the data it was not apparent that larger doses were more effective than 0.6 gm daily For maintenance of effect 0.1 to 0.2 gm was given each day after the patient left the hospital

*Use of Iodine* Except in two cases, iodine was not prescribed during the period of intensive thiouracil treatment until the basal metabolic rate had attained a normal level or until (in two cases) it was apparent that thiouracil was not benefiting the patients During maintenance treatment with thiouracil iodine in the form of syrup of hydriodic acid 1.0 cc each day was often added

## RESULTS

In 89 of the 100 cases exposed to the drug, treatment was completed in the sense that it was continued long enough to judge its effectiveness Success was estimated by the return of the basal metabolic rate to normal levels and by satisfactory control of other manifestations of the disease By these criteria there were 87 successes and two failures Two patients died of cardiac complications during the period of intensive treatment In nine of the 100 cases intensive treatment with thiouracil was abandoned because of unfavorable reactions which were or might have been attributable to the drug

*Failures* The two cases classified as failures are of considerable interest

R B, an intense Italian woman, aged 49, was said to have had a basal metabolic rate of +100 before admission She had received no iodine or other medication for the control of her thyrotoxicosis The first basal metabolic rate on the ward was +83 Three days later it was only +36 but on the day before treatment was started it rose to +52 She received 0.6 gm of thiouracil for 15 days, 0.8 for 8 days, 1.2 gm for 14 days At the end of 40 days her basal metabolic rate was still +56 She had gained no weight and the symptoms of thyrotoxicosis continued to be disturbingly severe Thiouracil was continued and a daily dose of 1.0 cc of syrup of hydriodic acid was added Five days later her basal metabolic rate was +61 She was transferred to the surgical ward where the basal metabolic rate was not materially influenced by discontinuance of thiouracil and hydriodic acid or by exhibition of larger doses of iodine (1.8 cc of Lugol's solution daily) In spite of her unfavorable condition, subtotal thyroidectomy was performed and was followed by an uneventful convalescence Contributory factors to failure may have been worry about money, worry about eight children, and a large nodular goiter Since there was no digestive disturbance it seemed unlikely that the lack of therapeutic effect could be attributed to a fault in absorption of the drug

O B was a worrisome, anxious woman of 44 who had serious hypertension as well as thyrotoxicosis. The hyperthyroidism had been recognized for four months. She had taken iodine until the time of her admission to New York Hospital. It was estimated that her thyroid gland was about six times normal size. The basal metabolic rate before treatment varied between +33 and +28. Treatment with thiouracil accomplished no obvious improvement. At the end of 28 days, her basal metabolic rate had risen to +40, her weight was essentially unchanged and symptoms of thyrotoxicosis were increasing. She was transferred to the surgical service where iodine was added to her treatment. After 28 days of thiouracil and 13 days of iodine and thiouracil her condition was not improved. Thyroidectomy was performed without untoward symptoms. Factors contributing to failure may have been previous iodination, the large size of the gland, hypertension and the patient's inability to adapt herself to her illness or her environment. No fault in absorption was apparent.

*Factors Influencing the Rate of Response* It was arbitrarily decided to discontinue intensive therapy when the basal metabolic rates had fallen to a range of between +15 and -10. The rapidity with which normal levels were attained varied between four and 108 days from the beginning of therapy. Beneficial effects of the drug were usually apparent within the first 10 days and by the fortieth day, the basal metabolic rate had returned to normal levels in over 80 per cent of the cases.

*Severity of Thyrotoxicosis* Factors influencing the rate of recovery were only partially evaluated. In general it appeared that the degree of initial thyrotoxicosis was not a reliable criterion. Although some of the most dramatic and satisfactory responses to the drug occurred in patients whose initial basal metabolic rates were greatly elevated, there were two with initial rates above +60 who required more than 60 days to attain normal levels.

*Size of Goiter* The size and character of the thyroid gland appeared to have some significance. The longest delays were encountered in cases with large nodular goiters. More often than not, response was prompt in patients who had small, diffusely hyperplastic glands. It was thought that this correlation might depend upon the amount of thyroid hormone which had been stored in the gland previous to the exhibition of thiouracil. Relative depletion of thyroxin might be expected in some of the small and very active glands whereas large and nodular goiters might have stored a large amount.

*Previous Iodine Medication* Response to thiouracil was on the average less prompt in those who had taken iodine in the immediately preceding period. More than one appeared to become somewhat worse for a time after iodine was discontinued and thiouracil started. One patient, Bc, who came to the metabolism ward in an extreme state of thyrotoxicosis after nine months of iodine had a very prompt response to thiouracil. This was not an isolated example. On the other hand in the following patient who responded most satisfactorily to iodine, there was a considerable delay in the benefit from thiouracil.

J M, a married woman of 32, was purposely given iodine in the form of 10 cc hydriodic acid each day for a period of two weeks. The iodine was then withdrawn



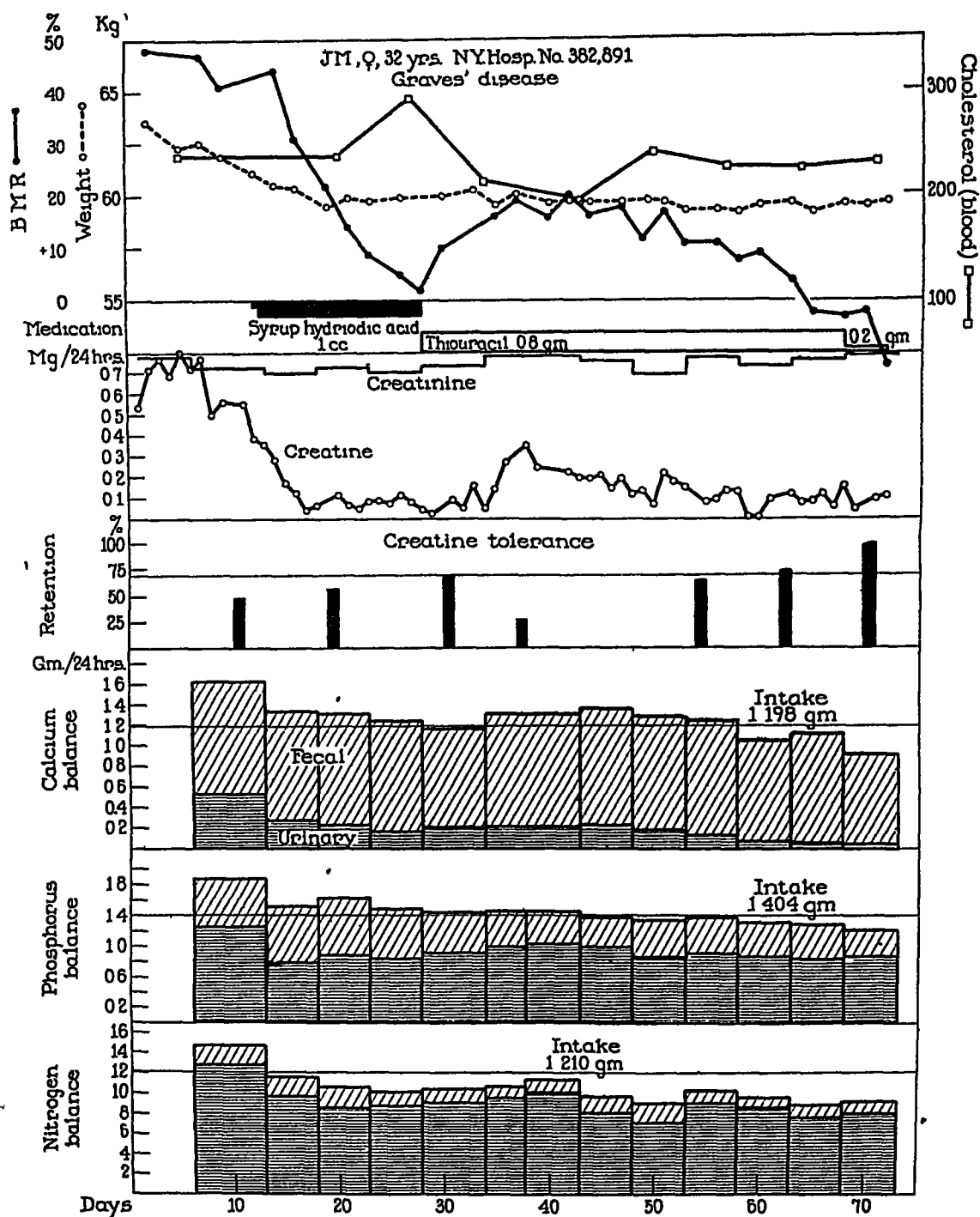


FIG 1 Chart of J M showing metabolic changes during the use of iodine and the later use of thiouracil

and thiouracil in daily doses of 0.8 gm was substituted. Progress was carefully observed in the metabolism ward. It will be seen in figure 1 that the response to iodine was prompt in terms of its effect on the basal metabolic rate as well as on the creatine metabolism. When, however, iodine was withdrawn there was a prompt release of iodine effect, with moderate relapse, indicated by rise in spontaneous creatinuria, diminution in creatine tolerance and elevation of basal metabolic rate. Actually 20 days elapsed, before the benefits of thiouracil were apparent, and more than 30

were required before the condition became as favorable as it had been when the iodine was discontinued

It is clear in this case that the benefit of iodine was lost before the action of thiouracil was established. The observations suggest also that for optimum control in this patient iodine should have been continued during the first few weeks of thiouracil treatment.

Perhaps the effect of preceding iodine medication upon the response to thiouracil depends upon its influence on the storage of thyroxin in the thyroid gland. This in turn is generally although not invariably related to the effect of iodination on thyrotoxic symptoms and the basal metabolic rate. It might be expected, therefore, that the more effective the previous iodination had been, the greater the likelihood of thyroid hormone storage and of delay in thiouracil effect. Thus, Be, who was uncontrolled by iodine manifested a very rapid response to the drug whereas in Ma, who had had remarkable improvement under iodine medication, the effect of thiouracil was delayed.

#### EFFECTS ON SYMPTOMS AND SIGNS OF THYROTOXICOSIS

*Weight* The emaciation of thyrotoxicosis was in most instances easily corrected. Two patients lost respectively 0.5 and 1.5 kg during the course of the treatment. In a few cases the weight remained stationary. Usually there was a striking gain often beginning after the first few days of treatment. Gains of from 5 to 10 kg were frequent. In one patient the weight increased 12.5 kg during two months of intensive therapy. Neither this nor other large gains in weight could be attributed to edema.

*Size and Character of the Gland* Because early observations in animals had demonstrated hyperplasia,<sup>2,3</sup> it was expected that beneficial action of the drug might be accompanied by demonstrable enlargement of the thyroid. Routine measurements during the period of intensive therapy failed to reveal important changes. The significance of slight variations was made less clear by gains in weight which might have been sufficient to increase the girth of the neck without enlargement of the gland. In no case during intensive therapy was there any change in size which could be regarded as disadvantageous to the patient. During the course of maintenance therapy, the gland in two patients increased in size and in one to such a degree that operation was thought to be necessary. Postoperative examination revealed an involuted gland with no suggestion of carcinoma and with few areas of hyperplasia. Thiouracil did not increase the firmness of the gland. Bruit and thrill if present before treatment were not diminished. In some cases the bruit increased in intensity and was loudest after most of the other signs of hyperthyroidism had disappeared. Gradually during maintenance therapy the bruit tended to disappear. In these cases administration of iodine without discontinuance of thiouracil caused increase in firmness of the gland and rapid subsidence of the bruit.

*Exophthalmos* Observations on the eyes of patients treated with thiouracil were of great interest. It was suspected that thiouracil might increase the degree of protrusion of the eyeballs not only because of the case of malignant exophthalmos encountered by Williams<sup>4</sup> but also because of the well attested facts that pituitary thyrotropic hormone tends to cause exophthalmos and that diminution in circulating thyroid hormone such as occurs during thiouracil therapy stimulates the production of thyrotropic hormone.

In none of the patients was there evidence that thiouracil diminished the protrusion of the eyeballs. On the contrary actual measurements indicated in some cases a recognizable increase in prominence. Although this seldom amounted to more than 2 mm on the Hertl exophthalmometer the increase in one case was as much as 4 mm. In no instance was the protrusion sufficiently great to cause troublesome symptoms, nor did the continuation of the drug ever result in progressive exophthalmos.

Although protrusion of the eyeballs was not favorably affected, spasm of the eyelids and the concomitant lid lag were diminished and in most of the cases entirely abolished. This led to the clinical impression that the exophthalmos had been greatly improved by the treatment and from a functional standpoint this was true. In one patient, who before treatment had extreme exophthalmos with bilateral corneal ulceration, the relaxation of lid spasm by thiouracil was apparently determinant in return of effective coverage by the lids and by the disappearance of corneal lesions.

The effects of thiouracil on eye symptoms are approximately those which have been observed following subtotal thyroidectomy. Recent careful exophthalmometry has demonstrated that protrusion of the eyeball tends to increase moderately following operation and that the improvement in eye symptoms long ascribed to surgery consists almost entirely in the control of lid spasm.<sup>5</sup>

*Effect on Tremor and Hyperkinesia* The fine intense tremor was promptly diminished by thiouracil and in most instances was entirely abolished. One of the most striking effects of the drug appeared in the elimination of the purposeless movements which are so characteristic of the thyrotoxic state. Even patients who before treatment had exhibited choreiform speech and athetoid motions rapidly attained a state in which the physical effects of emotion seemed actually less than normal.

*Circulatory Disturbances* In many patients, tachycardia and fall in both systolic blood pressure and pulse pressure paralleled the diminution in basal metabolic rate. This was by no means constant and some continued to display highly variable degrees of tachycardia and definitely elevated pulse pressure long after other symptoms of the disease had become quiescent. Palpitation as a symptom tended to disappear as the thyrotoxicosis subsided. Circulation rates increased to normal in patients whose hearts were not initially decompensated. Although the tendency was always toward improvement it can be said in general, however, that the circulatory phenomena

were too variable to offer reliable criteria of the effectiveness of the drug or of the degree of benefit to be derived from its use

Several patients in the group had cardiac arrhythmias and a few had serious rheumatic or coronary heart disease before treatment was started. No reversion of auricular fibrillation to normal rhythm could be attributed to therapy. One case of paroxysmal auricular flutter was entirely relieved of her attacks under the influence of thiouracil.

There were three deaths from cardiac disease during the course of treatment.

*Mc*, a man of 62 with arteriosclerotic heart disease and thyrotoxicosis, died of coronary occlusion during intensive therapy. On the second day of treatment with thiouracil he had a febrile reaction the cause of which was not determined but which led to discontinuance of the drug. A test dose of 0.1 gm. 15 days later was followed by no fever or other unfavorable reaction and after an interval of five days he was started on daily doses of 0.8 gm. of thiouracil. Three days later he died. Autopsy revealed evidences of atypical coronary occlusion.

*Mc*, a married woman of 28, had been known to have rheumatic heart disease with involvement of both aortic and mitral valves for many years before onset of thyrotoxicosis. Hyperthyroidism was easily controlled with thiouracil. During maintenance therapy, however, there developed increasing signs of heart failure which were imperfectly controlled by digitalis, mercupurin and rest. She died of cardiac decompensation five months after thiouracil treatment had been instituted. No autopsy was obtained.

The third patient who died of circulatory failure presented a complicated picture of disease which requires analysis and comment.

*Sh* was a woman of 60 who had suffered for four years from angina pectoris associated with hypertensive cardiovascular disease. For an undetermined period she had had an asymptomatic nodular goiter. She had also been correctly diagnosed and treated as a case of pernicious anemia. During routine treatment in the hematology clinic the basal metabolic rate was found to be +44 and she was admitted to the hospital. At that time she had severe anginal pain and shortly thereafter developed auricular fibrillation with increasing heart failure. She was treated with rest, digitalis and mercupurin and after 22 days had partially recovered compensation. It was at this time that thiouracil treatment was started. On the ninth day she developed fever with vomiting. The drug was discontinued. After an interval of 17 days she was given a test dose of thiouracil and since there was no reaction the drug was started again, in daily doses of 0.6 gm. Three days later she died suddenly. Autopsy revealed slight if any hypertrophy of the heart. There was, however, an extensive acute myocardial reaction with necrotizing coronary arteritis and periarteritis. The vessels themselves were not significantly thickened and there was no great amount of fibrous tissue in the myocardium but in many areas adjacent strands of muscle were separated by areolar tissue in which there was invasion of eosinophiles, polymorphonuclear leukocytes and histiocytes with a smaller number of lymphocytes. These changes were thought to be not unlike those found by Rich<sup>6</sup> in rabbits rendered sensitive to horse serum.

In evaluating this case it is perhaps important to emphasize that preceding thiouracil treatment there was a history of pernicious anemia and long standing angina pectoris and recent onset of auricular fibrillation and increas-

ing cardiac decompensation. This background suggests that death was attributable to causes other than thiouracil. The possibility cannot be excluded, however, that the acute myocardial lesions were caused by a sensitivity to the drug. This incident which occurred early in the use of the drug made us observe even more carefully the behavior of all patients under treatment with thiouracil and particularly of those having signs of cardiac disease.

*Serum Cholesterol* Initial levels of serum cholesterol in these thyrotoxic patients tended to be lower than normal although they were in themselves seldom diagnostic. Improvement in clinical symptoms and return of basal metabolic rate to normal levels was with an occasional exception as in J. M. in figure 1 accompanied by a corresponding elevation in cholesterol values. Determination of cholesterol, moreover, was found to be helpful in recognizing the onset of myxedema. An example of this may be seen in figure 2 where the cholesterol continues to rise while the basal metabolic rate remains stationary. In another case there were early symptoms of hypothyroidism at a time when the basal metabolic rate was still above normal. Two weeks later when the patient presented myxedematous swelling, changed voice, falling hair and dry skin the basal metabolic rate was still +14 but cholesterol was 433 mg per cent. In still another case of hypothyroidism induced by thiouracil it was found that the cholesterol values returned to normal coincident with the restoration of normal clinical behavior but at an interval of six weeks before a normal basal metabolic rate had been attained.

*Creatine Metabolism* Muscular weakness and defects in creatine metabolism are among the most constant manifestations of thyrotoxicosis. In only a few of the patients in this series was weakness extreme, but in all who were tested there was abnormality in creatine metabolism as shown by excessive spontaneous creatinuria, a reduced creatinine excretion and a diminished creatine retention after a test dose (1.32 gm). The character of the creatine defect and its prompt correction by thiouracil are shown in figure 2, which exhibits creatine and creatinine excretion as well as creatine tolerance tests before and after treatment.<sup>7</sup> In this case as in others similarly studied changes in creatine metabolism reflected benefit more promptly than did the basal metabolic rate or other criteria of improvement.

*Excretion of Nitrogen, Calcium and Phosphorus* Characteristic of thyrotoxicosis is a tendency to constant or intermittent excessive loss of nitrogen, calcium and phosphorus. Studies portrayed in figures 1 and 2 indicate the effect of thiouracil in reducing urinary and fecal excretion of all of these substances.

*Other Functions* Of the many tests performed routinely only a few revealed data of significance. Levels of blood urea nitrogen, total protein, albumin, globulin, calcium, phosphorus and alkaline phosphatase were unchanged by the drug. On the other hand the glycosuria of hyperthyroidism tended to disappear and the trend toward improvement was indicated in a

number of cases by lower glucose tolerance curves in the period after the drug had been given. One patient, a woman of 68, who had been taking 30 units of protamine insulin, was maintained without insulin, without dietary restriction, and with only occasional glycosuria for several weeks during

### Effects of Thiouracil on Graves' Disease Metabolic Effects

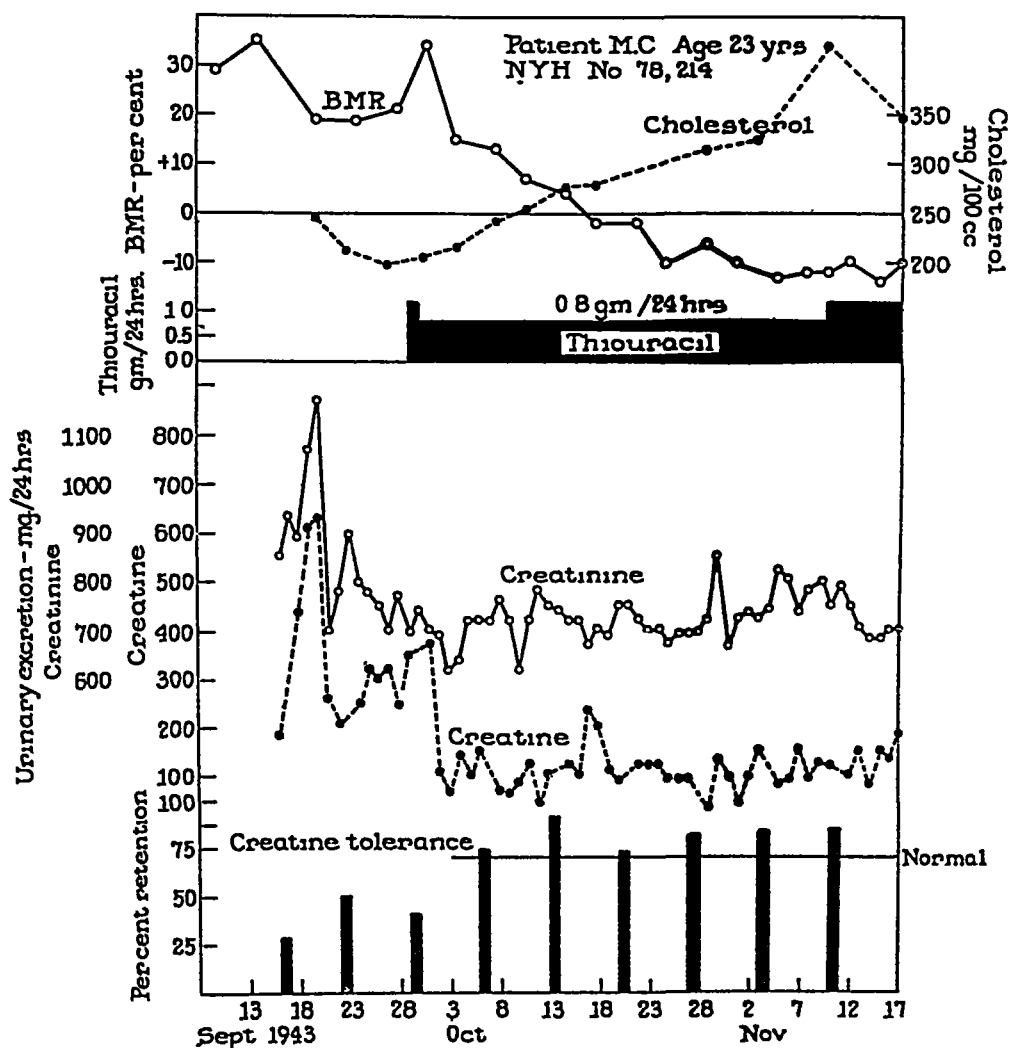


FIG 2 Chart of M.C. showing metabolic changes accompanying the use of thiouracil

intensive treatment with thiouracil. Later, however, massive glycosuria reappeared and during maintenance therapy insulin again became necessary for the control of a true diabetes.

**Behavior** In the majority of cases thiouracil accomplished a most profound transformation in the psychological state of thyrotoxic patients. Their agitation, their restless striving and their exaggerated reaction to

minor stimuli were replaced by a calm demeanor which at times appeared to be almost abnormal. Life situations which previously had caused them great perturbation or distress were accepted with philosophical composure. Their behavior seemed to suggest that under the influence of the drug some mechanism for usual emotional responses had been dulled or lost. A tendency of this kind was noted in many patients who did not display other evidences of hypothyroidism.

*Toxicity* All of the unfavorable reactions which developed in 100 cases treated with thiouracil are listed in table 2. In many instances great difficulty was encountered in deciding whether or not the untoward symptoms could be fairly attributed to the drug.

TABLE II  
Unfavorable or Toxic Reactions to Thiouracil

|                     |   |
|---------------------|---|
| Eruptions           | 8 |
| Fever               | 4 |
| Conjunctivitis      | 2 |
| Leukopenia          | 8 |
| Thrombocytopenia    | 1 |
| Nausea and vomiting | 1 |
| Jaundice            | 1 |
| Hematuria           | 1 |

*Eruptions* Erythematous, urticarial, and purpuric eruptions were encountered. The following abstracts illustrate the range of the lesions. The etiological rôle of thiouracil in the first four cases seems doubtful.

*Fo* Itching, red, punctate eruption over the abdomen occurred at the end of the first week of 0.4 to 0.6 gm daily doses of thiouracil. The drug was discontinued and iodine was substituted. There were no observations to substantiate the causative rôle of the drug. Subtotal thyroidectomy was performed on the twenty-fifth day.

*Ja* Urticaria which had been troublesome for several weeks before thiouracil treatment continued intermittently and irregularly after the drug was started. On two occasions administration of thiouracil during an interval free of urticaria was followed by an attack. During initial intensive treatment (0.4 to 0.8 gm daily) for 17 days, however, urticaria was not notably worse than it had been on occasions previous to the exhibition of the drug. After discharge from the hospital, giant urticaria developed during a period when iodine was substituted for thiouracil.

*Mi* Urticaria developed on the twenty-first day of treatment. Skin tests were negative to thiouracil. There was no recurrence for several weeks after resumption of the drug. A subsequent attack subsided when thiouracil was withdrawn but did not recur with resumption of treatment.

*She*, a woman of 25, received thiouracil in daily doses of 0.6 gm. On the fourth or fifth day of treatment she noted a few small papules, thickly dispersed over the thighs. At first this was thought to be ascribable to the drug but it was later found that its inception corresponded exactly with the first use of freshly laundered hospital pajama pants. Discontinuance of this apparel resulted in prompt disappearance of the eruption.

In the next two eruptions thiouracil appeared to be the causative agent.

*Ho* Fever and eruption developed on the tenth day of thiouracil treatment. The drug which had been administered in daily doses of 0.8 gm was discontinued. After

an interval of four days, it was again given, for two days in doses of 0.2 gm and for three days in doses of 0.4 gm. An eruption with edema then developed and terminated the therapeutic trial. A week later subtotal thyroidectomy was performed without incident.

*Ku*, a woman of 55 who had had two previous thyroidectomies, responded promptly to thiouracil and was maintained on 0.1 gm daily for a period of four months. She then began to complain of pains in her legs. A few days later an eruption was noted on the legs. The lesions were discrete, nodular, tender, slightly erythematous and extended over both anterior and posterior surfaces below the knees. They were exaggerated by standing or walking but did not disappear over a period of six weeks. Clinically they resembled erythema nodosum. Biopsy revealed no distinctive pathological features. At first the lesions were not ascribed to thiouracil. Finally, however, the drug was discontinued. The eruption gradually subsided but returned promptly with a test dose of 0.1 gm of thiouracil. The drug was withdrawn and subtotal thyroidectomy was performed.

The difficulty of judging the rôle of the drug in causation of eruptions is well illustrated by the following cases.

*Ra*. On the third day of treatment an erythematous eruption accompanied by 5 per cent eosinophilia occurred on the extensor surfaces of the arms and the flexor surfaces of the legs. Since this had not faded or changed after five days the drug was discontinued. In three days the rash had disappeared. Careful skin tests showed no local reaction to thiouracil. A test dose of 0.1 gm was then given since no unfavorable symptoms developed. A test dose of 0.2 gm caused no eruption. Intensive treatment with 0.6 gm daily was reinstituted and continued for 17 days, without untoward event. The eruption then reappeared. The drug was withdrawn for three days but when the rash faded was again given in dosage of 0.6 gm until the hyperthyroidism was entirely controlled. Maintenance therapy was continued for six months thereafter. During this entire period there were no dermatological manifestations.

*Ch*. An anxious excitable woman of 27 had with thiouracil therapy a satisfactory remission which was maintained on doses of 0.1 gm for a period of four months. At the end of this time she suffered a partial relapse which was controlled by increasing the dose to 0.2 gm. Two months after starting the larger dosage a purpuric eruption was noted. This was greatest on the legs but was also seen as a few discrete patches on the arms. It continued for five days before thiouracil was withdrawn. In three days the eruption had faded. She then took phenobarbital for sleeping and the following morning the eruption had reappeared. Thiouracil was started again in doses of 0.1 gm four times daily and was continued for three days without event. Then a leukopenia of 3,000 without granulocytopenia and with sharp increase in immature granulocytes was noted and the drug was withdrawn. Later a test dose of 0.1 gm of thiouracil caused no symptoms but 0.2 gm was followed promptly by reappearance of purpuric eruption. With this there was a slight fall in leukocytes without granulocytopenia. Subtotal thyroidectomy was advised. Test doses of 0.1 and 0.2 gm a few days later caused no symptoms. Nevertheless subtotal thyroidectomy was advised.

Eruptions thus afforded occasion for discontinuing treatment in four cases. In two of these (*Ho* and *Ku*) the causative rôle of thiouracil appeared to be approximately established.

*Fever*. An elevated temperature of undetermined origin occurred in *Mc* and *Sh*, patients who as already mentioned died of circulatory failure. Fever



was also encountered as an accompaniment of eruption in Ho. It was the cause of discontinuance of treatment in the following case

*L<sub>1</sub>*, a woman of 50, had an unexplained fever ranging between 36.6° and 38° C during a control period preceding therapy. During the first 10 days of the thiouracil treatment fever of similar degree continued. On the eleventh day it reached a level of 38.8° and on the fourteenth when the drug was discontinued the afternoon temperature was 39.8°. Thirty hours later the temperature was normal. For the next three days it ranged between 37° and 37.8°. A test dose of 0.2 gm of thiouracil was then given and was followed by an immediate rise in temperature which subsided in 24 hours, and remained normal for 10 days when a test dose of 0.1 gm was followed by a fever of 38.4°. During these exacerbations the white blood cell and differential count did not change significantly and at no time did they indicate the presence of infection.

It was of special interest that the basal metabolic rates which during thiouracil treatment had been elevated above the level during the control period, fell immediately to normal after the drug had been withdrawn. This suggested the possibility that the drug was successfully affecting thyroxine production even when it was producing toxic reactions in the patients.

#### *Conjunctivitis*

*Re* A troublesome conjunctivitis which developed during treatment pursued a variable course with continuance of thiouracil. Evidence that it was independent of the use of the drug came chiefly from the fact that there were several spontaneous remissions during the period when the dosage of the drug was being increased.

*S<sub>1</sub>* A bilateral conjunctivitis of moderate severity twice subsided when the drug was discontinued and twice recurred promptly with its exhibition. It was then decided that the drug should be permanently withdrawn. The spontaneous reappearance of the conjunctivitis after an interval of a week following discontinuance of the drug cast serious doubt on the etiologic relationship.

*Leukopenia and Granulocytopenia* The fear of agranulocytosis pervaded the entire study. Hundreds of white blood cell counts showing normal values were performed. Considerable variations were encountered and slight temporary leukopenias even to 3,000 were not uncommon. In several instances a fall in the total count was accompanied as in Ch by an increase in the number of immature granulocytes. In most cases, the percentage of granulocytes remained essentially unchanged with minor reductions in total white blood cell count.

In three cases exhibiting leukopenia without granulocytopenia treatment was continued cautiously but intermittently. No correlation of white blood cell count and dosage of drug could be established. The following case is an example.

*S<sub>III</sub>*, a woman of 49, had severe thyrotoxicosis complicated by bronchiectasis. During both control and treatment periods she had a moderate fever which seemed to be ascribable to her pulmonary condition. On the fourteenth day treatment was interrupted because of fall of white blood cell count to 2,700 with 65 per cent mature and 10 per cent immature granulocytes. The count returned rapidly to normal and remained at normal levels following resumption of thiouracil six days later.

On three occasions leukopenia without granulocytopenia was the reason for abandoning treatment

*Ol*, a woman of 50, was treated on the surgical service and was given iodine for 40 days without evidence of benefit. She was then given a test dose of thiouracil. Before the test the white blood cell count was 4,300 with 60 per cent of granulocytes. Immediately following thiouracil the total count was the same but the granulocytes were recorded as 32 per cent. The drug was discontinued. During a period of 25 days in which no treatment was given the white blood cell count varied between 3,300 and 6,000 and the granulocyte count between 26 and 60 per cent. Thiouracil was then given for 12 days in daily doses of 0.8 gm with variations in white blood cell count from 4,700 to 5,500 and in granulocytes from 54 to 60 per cent. Subtotal thyroidectomy was performed without event at the end of this period.

*Rn* was treated on the surgical service. On the twelfth day of thiouracil a fall in the white blood cell count to 4,000 with 62 per cent of granulocytes was considered sufficient reason for withdrawal of drug and substitution of Lugol's solution. No tests were made to determine sensitivity.

*Wyn*, a woman of 26, had received 35 days of thiouracil treatment with satisfactory control but without complete remission. Her white blood cell count which had been variable then fell to 4,400 with 20 per cent mature and 14 per cent immature granulocytes. The drug was discontinued without further testing and she was transferred to the surgical service.

The following two cases present in bold relief the hazards of thiouracil therapy. The first is particularly terrifying because agranulocytosis developed under close observation in a hospital ward, the second because serious granulocytopenia preceded the appearance of any recognizable symptoms.

*Rcb*, a woman of 57, had had two previous subtotal thyroidectomies with later recurrence of thyrotoxicosis. In the summer of 1944 she was treated with thiouracil in the Metabolism Ward. The record of her white blood cell count may be seen in figure 3. During the first 10 days of therapy her white blood cell count varied between 5,400 and 7,000 with no granulocytopenia. On the eleventh day following a short period of nausea and slight fever it fell to 2,300 without significant change in the total granulocyte count. As in several other cases during periods of leukopenia the relative number of immature granulocytes increased in this instance from 4 per cent before to 24 per cent after the development of leukopenia. The drug was discontinued for a period of nine days. Test doses were administered without the development of alarming symptoms. For 25 days thereafter she received daily doses of 0.6 gm of thiouracil without the appearance of disturbing symptoms. Remission, however, was delayed and it was decided to withdraw thiouracil. She refused to submit to another operation and she was discharged from the hospital on a sufficient dose of iodine. On this regime she gradually lost weight and gradually became more nervous until in February 1945 she was again severely thyrotoxic. Again she refused thyroidectomy. She was therefore readmitted to the hospital where she was given under careful supervision 0.2 gm thiouracil each day. Again the white blood cell count varied (see figure 3) from 2,600 to 5,400 with granulocyte counts from 50 to 56 per cent. On the twenty-first day of treatment the white blood cell count fell to 2,000 cells with only 2 per cent granulocytes. Thiouracil was discontinued and the following day the white blood cell count was 700 with 1 per cent granulocytes. The pharynx became fiery red, the right tonsil protruded, the temperature rose to 40.1° C., prostration was extreme. Treatment consisted of penicillin in doses of 25,000 units

every two hours with a great number of remedies aimed at stimulating regeneration of white blood cells. Included were daily intravenous injections of 100 cc of crude liver extract in 1,000 cc of normal saline and daily doses of 10 cc of folic acid, 0.2 gm of pyridoxin and three capsules of yellow bone marrow concentrate. She also received several transfusions and two doses each of 10 cc of pentnucleotide. Within 24 hours of the beginning of this treatment the clinical picture was remarkably changed. The pharynx became less inflamed. The right tonsil receded. Prostration was less profound. The temperature fell to 38° C. She remained in this state for seven days without any evidence of improvement in her agranulocytosis. On the seventh day sternal puncture showed 4,200 white blood cells. Most of these were premyelocytes. There were many myeloblasts and megakaryocytes. Several lymphoblasts and normoblasts were seen but only one polymorphonuclear cell could be found.

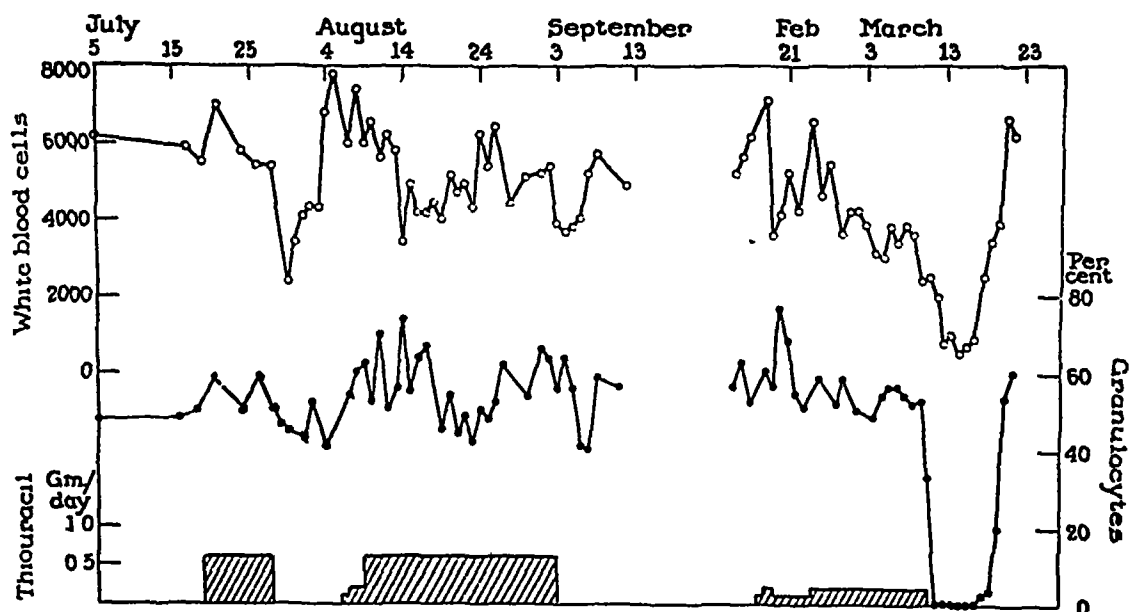


FIG 3 Record of changes in white blood cells and granulocyte count during thiouracil treatment in Reb

The following day granulocytes began to appear again in the peripheral blood and she made a rapid and complete recovery. She was later subjected to subtotal thyroidectomy without untoward incident.

It was believed that her life had been saved by the protection which penicillin afforded against the development of serious infection. One could not be encouraged to think that the other remedies had had significant effect upon the rate of regeneration of the bone marrow.

*Pc*, a boy of 16, was treated with thiouracil in the autumn of 1944. Therapy was strikingly successful and he was discharged on maintenance dosage. Because of misunderstanding he discontinued the use of the drug after one month and absented himself from the clinic. In April 1945 he reappeared with relapse. He was started on 0.2 gm of thiouracil per day without readmission to the hospital. Two weeks later his hyperthyroidism was under partial control, he showed no clinical signs of toxicity but his white blood cell count was found to be only 3,000. He left the clinic before a differential count could be done and could not be located until two days later when his count was 4,900 but with 2 metamyelocytes, 5 band cells and only one mature granulocyte. He still showed no symptoms or clinical signs of toxicity. Thiouracil was withdrawn and the following day he developed sore mouth and a pustule on his ankle. He was given penicillin. His white blood cell count returned to normal in 4 days. The mouth lesions and skin infection healed promptly.

### *Thrombocytopenia*

*Ms*, a woman of 40, was treated with daily doses of 0.6 gm of thiouracil for 12 days. It was then noted that the platelet count was low—32,000—and that application of the tourniquet caused appearance of moderately extensive purpura in the skin peripheral to the constriction (positive Rumpel-Leeds test).

Bleeding time was normal but clotting time was prolonged 20 minutes and 30 seconds by the Lee and White method. Three check platelet counts and inspection of the smear confirmed the original observation. There was no evidence of abnormality in red blood cells or white blood cells. Drug was withdrawn. Platelets promptly (48 hours) rose to 240,000. Thiouracil was again exhibited after 10 days and was continued without incident in doses of 0.1 gm four times daily until basal metabolic rate became normal. Platelet count remained normal. Rumpel-Leeds test was variable but for the most part normal.

### *Nausea and Vomiting*

*Wal*, a high strung, apprehensive young woman, developed, after four days of treatment, nausea and vomiting which were the occasion of withholding the drug for five days. Renewal of medication in 0.8 gm and later 1.0 and 1.2 gm caused no gastrointestinal symptoms.

### *Jaundice*

*Ro*, a woman of 52, was treated early in the series. The drug was given in amounts varying from 0.6 to 0.8 gm daily for a period of 21 days. She then noted some anorexia and nausea. The following day she was obviously jaundiced. Thiouracil was discontinued. Icterus index rose to 23, but in 10 days the jaundice had disappeared. Iodine was started at the time thiouracil was stopped. No effort was made in subsequent course to give thiouracil although there was a partial relapse of thyrotoxicosis after discharge from the hospital. Icterus indices obtained after discharge from the hospital and long after discontinuance of thiouracil were intermittently above normal values.

This incident was responsible for studies of icterus index and prothrombin values on all patients treated thereafter. No significant changes were encountered and doubt persisted whether the jaundice in this case could be justly attributed to thiouracil.

### *Hematuria*

*Wa*, a hypertensive middle-aged man with electrocardiographic changes suggestive of coronary occlusion, had basal metabolic rates which ranged from +24 to +30 and were little influenced by iodine. Thiouracil was exhibited in daily doses of 0.6 gm for 5 days. He then developed a frank hematuria. There was no crystalluria and no cause for the bleeding was discovered but because of other features of the case it was decided to abandon treatment. The patient died two months later in circulatory failure. Autopsy was denied.

*Comment* In considering these 26 untoward incidents, it is impossible to establish definitely the etiological relationship of the drug. In our own estimation a total of five including the two previously mentioned eruptions (*Ho* and *Ku*), one febrile reaction (*Li*), and two granulocytopenias (*Rc* and *Pe*) were regarded as probably or certainly ascribable to the drug.

## RESULTS OF MAINTENANCE THERAPY

*Production of Myxedema* A recognizable hypothyroidism developed in five patients during maintenance therapy. The more significant data concerning them may be seen in table 3. In three of the five cases thyrotoxicosis preceding treatment had been of severe grade. In the other two cases the initial basal metabolic rates were respectively +20 and +25. In one case the first symptoms became apparent within three weeks of completion

TABLE III

| Patient        | Sex | Age | Initial<br>B M R | Time of Onset<br>from Start of<br>Treatment<br>(Months) | Time of<br>Recovery<br>following<br>Cessation of<br>Treatment<br>(Months) | Subsequent<br>Course |
|----------------|-----|-----|------------------|---|---|----------------------|
| B <sub>1</sub> | F   | 45  | +72              | 2   | 1   | Relapse<br>operation |
| G <sub>a</sub> | F   | 46  | +54              | 4½  | Now<br>recovering   |                      |
| Be             | F   | 32  | +72              | 6½  | 1   | Relapse              |
| Ze             | F   | 32  | +20              | 4   | 1   | No relapse           |
| Ne             | M   | 58  | +25              | 2   | 6   | No relapse           |

of the intensive therapy. In a second they were evident in the second month of treatment. Maintenance had been continued for 2 to 6½ months in the other patients before symptoms of hypothyroidism were noted. Notes on three of the cases are illustrative of the mode of onset as well as the development and persistence of myxedema.

*B<sub>1</sub>* was a woman of 45 with severe thyrotoxicosis complicated by bronchiectasis. Intensive treatment with thiouracil accomplished an excellent result. At the time of her discharge from the hospital her basal metabolic rate was normal but she was complaining of puffiness about the eyes and of a stiffness and full feeling in the arms and hands. A month later, on a maintenance daily dosage of 0.1 gm, she had become obviously and uncomfortably myxedematous with characteristic appearance, dry skin, cold extremities, harsh voice, and impaired hearing. It is notable that while the cholesterol level in her serum had risen to 433 per cent her basal metabolic rate was still within the upper range of normal, +14. The drug was immediately withdrawn. A few weeks later she developed pneumonitis about her bronchiectatic cavities. The thyrotoxicosis recurred. She was discouraged about resumption of thiouracil therapy and was subjected to a successful and uneventful subtotal thyroidectomy.

*Be* was a woman of 32 with recurrent severe thyrotoxicosis. Intensive therapy with thiouracil was most successful and she was easily maintained in a normal state on 0.2 gm thiouracil daily. In the fourth month of her treatment she took a trip to Cuba. When she returned six weeks later she was complaining of stiffness in arms and hands, and of some puffiness about the eyes. Three weeks later her appearance was characteristically myxedematous. Her skin was dry, her hair was falling, her voice was hoarse and her speech was slow and indistinct. Cholesterol had risen to a level of 468 mg per cent. Upon discontinuance of the drug, her basal metabolic rate returned rapidly to normal, and symptoms of myxedema disappeared. Within two months thyrotoxicosis was again apparent but was easily controlled by resumption of thiouracil.

Ne was a man of 58 with moderate thyrotoxicosis and a basal metabolic rate of only +25. He was treated with 0.6 to 0.4 gm of thiouracil daily for 31 days. Intensive therapy was discontinued when the basal metabolic rate reached normal. On a maintenance dose of 0.2 gm daily the rate continued to fall to -18. Classical signs of myxedema were apparent by the sixtieth day of treatment when the cholesterol had risen to 372 mg per cent. The drug was then discontinued but signs and symptoms of hypothyroidism persisted. For a time it was thought that the drug might have permanently prevented the formation or mobilization of thyroxine. After six months, however, the symptoms of myxedema gradually disappeared and the patient attained and maintained what appeared to be normal thyroid function. It was of interest that again the level of cholesterol followed more closely the clinical symptoms than did the metabolic rate and that the cholesterol values attained normal levels before the basal metabolic rates.

Certain aspects of these cases were of special interest. It was apparent that the onset of hypothyroidism was not dependent upon the initial degree of thyrotoxicosis. The basal metabolic rates before treatment ranged in different patients between +20 and +72. The development of myxedema did not indicate immunity to later relapse and it is notable that after withdrawal of the drug three of the six cases passed by imperceptible stages from clinically complete myxedema through the normal range to moderately severe hyperthyroidism. Determinations of cholesterol in the serum were found to be of great value in predicting both the onset and the offset of myxedema. In several instances they were shown to parallel the clinical picture more closely than did the basal metabolic rates. The speed with which the edema and major clinical symptoms of hypothyroidism could develop was a matter of considerable surprise. On two occasions patients who presented only doubtful or equivocal signs of diminished thyroid function became dramatically myxedematous within an interval of three weeks.

TABLE IV  
Thyroidectomy Following Thiouracil Treatment

| Patient        | Duration of Thiouracil Treatment | Reason for Discontinuing Thiouracil       | Operative Procedure | Outcome of Operation |
|----------------|----------------------------------|---|---------------------|----------------------|
| B <sub>1</sub> | 2                                | Relapse following myxedema                | Uneventful          | Satisfactory         |
| Pe             | 2                                | Toxicity                                  | Uneventful          | Satisfactory         |
| Pr             | 6½                               | Projected travel without adequate control | Hemithyroidectomy   | Satisfactory         |
| Ku             | 10                               | Toxicity                                  | Uneventful          | Parathyroid tetany   |
| S              | 7                                | Toxicity                                  | Uneventful          | Satisfactory         |
| Be             | 6½                               | Projected travel                          | Uneventful          | Satisfactory         |

*Thyroidectomies* In the entire series there were 14 thyroidectomies. Of these eight were performed either because of failure of the drug to benefit (B<sub>n</sub> and B<sub>u</sub>) or because of toxic reactions during intensive therapy. The other operations were performed for a variety of reasons during the period of maintenance. In table 4 the causes of interruption are listed. It will be

noted that in three instances (Pe, Ku and Sl) the operation became necessary because of toxic reactions whereas in the others it was chosen either because of relapse (B<sub>1</sub>) or because of projected travel which would prevent the patient from receiving adequate medical supervision

All patients were given iodine for a period of at least 10 days before operation. No unusual surgical difficulties were encountered although several glands were vascular and relatively friable. The postoperative course was uneventful and no patient presented evidence of thyroid storm. One patient who had had three previous thyroidectomies developed parathyroid tetany several weeks after the operation.

*Relapse during Treatment* Two patients relapsed while on maintenance doses and in one of them increase in dosage to 0.6 gm daily for a period of 37 days was insufficient to restore satisfactory control. The factors determining the relapse were not apparent in either case. Variations in state were encountered in many of the patients and on several occasions it was necessary to vary the dose of thiouracil from 0.1 to 0.2 gm to maintain an optimum state.

*Withdrawal of Drug during Remission* In 48 of the 87 patients exhibiting satisfactory remissions the drug has been discontinued. The experience of Astwood<sup>7</sup> led us to expect that remission of symptoms would not be maintained if thiouracil were withdrawn soon after normal conditions were attained. It was planned, therefore, to continue thiouracil for a minimum of six months, from the time of its first exhibition or longer if the control seemed too precarious at the end of that time.

TABLE V

| Patient        | Reason for Stopping Treatment | Length of Time Treated, Months | Initial Basal Metabolic Rate | Relapse | Time of Relapse, Months |
|----------------|-------------------------------|--------------------------------|------------------------------|---------|-------------------------|
| Ne             | Myxedema                      | 2                              | +25                          | No      | —                       |
| B <sub>1</sub> | Myxedema                      | 2                              | +72                          | Yes     | Immediate               |
| Ze             | Myxedema                      | 4                              | +20                          | No      | —                       |
| Ga             | Myxedema                      | 4½                             | +54                          | —       | —                       |
| Dr             | Not available for treatment   | 3                              | +25                          | No      | —                       |
| Pe             | Not available for treatment   | 2                              | +13                          | Yes     | 3                       |
| Co             | Not available                 | 2                              | +25                          | Yes     | 17                      |
| Le             | Coronary accident             | 2                              | +26                          | No      | —                       |
| She            | Pregnancy                     | 1                              | +23                          | No      | —                       |
| Fr             | Pregnancy                     | 5                              | +40                          | No      | —                       |
| Sm             | Condition justified           | 5½                             | +                            | Yes     | —                       |
| Fa             | Condition justified           | 5                              | +10                          | No      | —                       |
| Su             | Condition justified           | 3                              | +36                          | No      | —                       |

This intention could not be followed strictly in all cases and there were 13 whose treatment was interrupted for one reason or another before six months had elapsed. These cases are listed with some pertinent data in table 5.

It will be noted that they include four of the five cases which developed myxedema. Another patient (Dr) became too busy with her family to permit sufficient observation so therapy was discontinued without relapse at the end of the third month. Another (Pe) absented himself because of misunderstood directions. Another (Co) quit treatment after three months and was lost to view until 17 months later when she had developed a moderate relapse. It is perhaps significant that this relapse followed a period of considerable distress when her parents took to drink, her child became ill, her sister developed Graves' disease and her husband who had fallen in love with another girl asked for a divorce. The drug was discontinued during a coronary occlusion in Le and was not started again because he never showed any tendency to relapse of thyrotoxicosis. Treatment was withdrawn in patients (Sh and Fr) because of pregnancy. This was done because animal experiments had indicated possible danger of the drug to the development of the fetus,<sup>9</sup> and in spite of clinical experience that thiouracil in pregnancy may not always be demonstrably harmful.<sup>10</sup> In three others (Sin, Ta, Sn) the condition was so satisfactory that a full six months treatment was not considered necessary.

TABLE VI

| Patient | Duration of Treatment, Months | Reason for Withdrawal of Drug | Interval between Withdrawal and Relapse, Months | Apparent Exciting Cause of Relapse | Subsequent Course                 |
|---------|-------------------------------|-------------------------------|---|------------------------------------|-----------------------------------|
| Bi      | 2                             | Myxedema                      | 1   | Bronchiectatic pneumonitis         | Subtotal thyroidectomy            |
| Sm      | 5½                            | Satisfactory state            | 1   | Bronchiectatic pneumonitis         | Controlled by thiouracil          |
| Pe      | 2                             | Unavailable for treatment     | 3   | None discovered                    | Subtotal thyroidectomy            |
| Co      | 2                             | Unavailable for treatment     | 17  | Family difficulties                | Still under trial with thiouracil |
| Ba      | 8                             | Satisfactory state            | 12  | Anxiety state                      | Controlled by thiouracil          |
| Sl      | 7                             | Toxic reaction                | 1   | Anxiety state                      | Subtotal thyroidectomy            |
| Br      | 6½                            | Satisfactory state            | 4   | Psychological trauma               | Subtotal thyroidectomy            |
| McA     | 9                             | Satisfactory state            | 1   | Insecurity                         | Controlled by thiouracil          |
| Ku      | 10                            | Toxic reaction                | 1   | None discovered                    | Subtotal thyroidectomy            |
| Be      | 6½                            | Myxedema                      | 1   | None discovered                    | Controlled by thiouracil          |
| Coh     | 7                             | Satisfactory state            | 2   | Sudden psychic trauma              | Controlled by thiouracil          |

For the whole series the longest time of withdrawal without relapse has been 16.5 months. In another case the interval has been 15 months while in four others it has been more than 10 months. The average time has been 6.1 months and only six cases have been observed for less than two months following the cessation of treatment.



In this entire group of 48 there have been thus far only 11 relapses (22.9 per cent). These are listed with some pertinent data in table 6.

Four of the relapses occurred in patients (B<sub>1</sub>, Pe, Co, Sm) who had received the drug for less than six months. One (Pe) had been treated with thiouracil for only two months. Two (B<sub>1</sub> and Sm) relapsed during an exacerbation of bronchiectasis. Family difficulties, anxiety states or insecurity may have contributed to several (Co, Ba, Pr, McA, Sl). Relapses occurred in two patients (Kn and Be) who had had previous thyroidectomies and had previously shown marked tendency to recurrence of the thyrotoxic state. The relapse of the last case deserves special mention because of the mechanisms it reveals.

Coh, a hard working florist, emotional, sensitive, and severely thyrotoxic, had been treated by thiouracil with great success. He continued this treatment for seven months. At the end of this time his condition seemed to justify withdrawal of thiouracil. For two months there was no sign of relapse. Then one day, he was coming home from work when he saw a crowd gathered near his house and heard the frantic cries of his young son. Thinking that his boy had met with some frightful accident he ran to where the crowd was gathered, found that his own son was not injured but that a neighbor's boy had suffered a compound fracture from being run over by an automobile. He picked up the boy, carried him home, up two flights of stairs and stood by until the doctor came. That night he could not sleep. The following day he was nervous and distraught. When he presented himself three weeks later he displayed all the evidences of a serious thyrotoxic relapse. Use of thiouracil in doses of 0.2 gm without interruption of work permitted a satisfactory remission. This was the more remarkable since it took place during the Christmas season when his work as a florist required long hours and arduous labor.

In observing patients following the withdrawal of therapy, it was often difficult to determine whether variations in mood and activity were indicative of relapse. On several occasions there was strong temptation to start the drug again in patients who later had complete remission of all suspicious symptoms. There can be little doubt that in thyrotoxic patients who have undergone remission following the use of thiouracil there is always the tendency to relapse.

TABLE VII

|  |    |     |
|--|----|-----|
| Number of Cases Treated                                |    | 100 |
| Unsatisfactory or questionable results                 |    | 27  |
| Failed to respond                                      | 2  |     |
| Died of cardiac complications                          | 3  |     |
| Treatment interrupted because of unfavorable reactions | 12 |     |
| Relapse during therapy                                 | 4  |     |
| Unsatisfactory control during maintenance              | 2  |     |
| Treatment interrupted because of growth of gland       | 1  |     |
| Treatment interrupted by choice of patient             | 3  |     |
| Satisfactory results                                   |    | 73  |
| Satisfactory remission with continuance of therapy     | 36 |     |
| Continued remission after cessation of therapy         | 37 |     |

*Continued Maintenance* Of the entire group there are 36 patients still under maintenance therapy. Of these there are two whose treatment has been continued for 12 months and 18 months respectively because their re-

mission was precariously and imperfectly controlled. The others have not yet completed six months of therapy.

*Résumé* In table 7 there is presented a summary of results in the 100 cases. It will be seen that 73 of these are regarded as successful in the sense that remissions have continued during maintenance doses of the drug, or after the drug has been discontinued. Twelve represent flat failures in that the drug either failed to act, relapse occurred during maintenance treatment or patients were not maintained in a satisfactory state. The other cases designated as unsuccessful in table 7 are more difficult to assay in that they represent situations which may or may not have required discontinuance of drug and substitution of other therapy.

### DISCUSSION

*Efficacy of Thiouracil* In 73 of the 100 cases the drug has been successful in the sense that it has produced satisfactory remission for periods up to 21 months. It has failed in 14 cases either because it did not control thyrotoxic symptoms or did not maintain the patient in a satisfactory condition. During the course of treatment there were three deaths ostensibly from circulatory complications. None of them could be fairly ascribed to the drug nor did it seem likely that the patients would have been saved by other methods of management. The administration of the drug has been accompanied by 26 unfavorable reactions at least five of which can be attributed to toxic action of thiouracil.

With such a record it is appropriate to ask again whether the drug should be made generally available, whether it can be expected under any circumstances to offer a permanent cure and to what extent it may be used as a substitute for surgical treatment. Some of the data can be used in a partial answer.

*Safety for General Use* The chief reason now recognized for withholding thiouracil from general use is the danger of agranulocytosis. Experience of reported cases has shown that the occurrence of this serious complication is, within the therapeutic range, not dependent upon the dosage of the drug but is more properly considered as an idiosyncrasy or special sensitization. Circulatory agranulocytosis may precede by several hours the development of any recognizable clinical symptoms and may occur so suddenly that it cannot be forestalled even under the meticulous observation of a well conducted ward. It appears, therefore, that the danger exists even with the most careful management. It is questionable whether the incidence of intoxication is increased by any except the most flagrant abuses. Evidence that this is true is furnished by comparison of Williams' <sup>4</sup> results on ambulant patients with those we have obtained with a group carefully guarded in a hospital ward. It is not apparent that the greater supervision resulted in fewer accidents or more favorable therapeutic results.

One must recognize also that the drug has already been extensively dis-

tributed and has been used under widely variant degrees of scrutiny with a resultant mortality which, though deplorable, may be no higher than that incident to the best of other methods of treatment. Arguments of this kind may justly be advanced in favor of acceptance and a more general distribution of the drug. They must not, however, be used as an excuse for lax supervision of those who receive thiouracil. Consideration of our patient Re demonstrates how urgent and how life saving early recognition and prompt treatment may be after agranulocytosis has developed.

*Permanence of Remission* Evidence is not yet sufficient to state whether thiouracil can cause permanent remission or cure of thyrotoxicosis. In this series, it is significant that of 47 cases in which the drug was withdrawn for periods from one to 16 and one-half months after two to seven months of treatment there have been only 11 or 23.4 per cent of relapses. All experience with thyrotoxicosis has indicated that those who have once had the disease have a constant or intermittent tendency to relapse. Although this generalization may apply to all thyrotoxic patients, the tendency has been so marked in a few that repeated thyroidectomy has become necessary. Because the tendency to recurrence has been obvious, it is somewhat surprising that so crude a procedure as the removal of an entirely empiric amount of functioning thyroid tissue should so often accomplish satisfactory permanent control.

Since in patients treated with thiouracil no tissue is removed and since production of thyroxin commences soon after the drug is withdrawn one might predict almost immediate relapse when treatment is discontinued. That this does not occur suggests the thesis that effective control of thyrotoxicosis may depend less upon removal of functioning tissue than upon the more or less prolonged interruption of functional disturbances and of vicious cycles of reaction and behavior. That the tendency to relapse persists after thiouracil treatment is attested by the 11 recurrences which we have observed at variable intervals after withdrawal of the drug. In some of the initially more severe cases and particularly in those who had relapsed after previous thyroidectomy recurrence of symptoms started almost as soon as treatment was stopped. In other cases including some of apparent severity, relapse was delayed, in one instance as long as 17 months. Such evidence as has been accumulated in our short series indicates that an important rôle in the timing or in the occurrence of relapse may be played by such factors as insecurity, anxiety states, violent psychic trauma and infection.

*Thiouracil as a Substitute for Surgery* It does not need to be emphasized that any new remedy for thyrotoxicosis must be good to replace the accepted iodine preparation and operation where operative mortality in the best hands may approximate 1 per cent and where a single thyroidectomy may accomplish control satisfactorily enough to avoid subsequent operations in possibly 85 per cent.<sup>11</sup> Actual relapse rate following surgery is unknown since many patients who have received thyroidectomy are seen only occasionally thereafter. In careful follow-up on small groups many minor and transient relapses are seen.

While it is too early to know whether mortality rate from the accidents of thiouracil is as great as that consequent to the best surgery, it is safe to say that it has been less than the average mortality in thyroid surgery throughout the country. In the 48 patients from whom thiouracil has been withdrawn in this series, 76 per cent have not yet relapsed. It will be seen that this record approximates but does not equal that usually claimed for surgery.

There are a number of relative disadvantages in thiouracil therapy. The period of intensive treatment with the drug is usually more time consuming. In a few cases it approximates the month of treatment which constitutes successful iodine preparation, operation and postoperative convalescence. More often it requires between 30 and 40 days and in a few cases intensive treatment for two or three months may be necessary. This is a matter of considerable consequence if the patient is to be hospitalized during intensive therapy. If as appears possible from Williams' experience<sup>4</sup> thiouracil can be given with relative safety to ambulant patients, the matter is not of so much consequence.

It appears at present, however, that intensive treatment should be followed by several and possibly by four or five months of maintenance therapy during which danger of toxicity still looms as a rare but ominous hazard. Such a course requires much more constant observation and careful scrutiny than does postoperative care. It requires also a high degree of cooperation on the part of the patient, and this is maintained with increasing difficulty as the treatment is prolonged. The complexity of life interposes many circumstances such as employment, family duties and travel which make exact control over long periods difficult or even impossible. Also in young women pregnancy may interrupt the course of treatment before control or optimum effects have been established.

Our own experience as well as that of the literature indicates that large nodular goiters respond less readily to thiouracil and that some of them are extremely resistant to treatment. This fact as well as esthetic considerations and cancer control favor surgery as the treatment of choice in such cases.

On the other hand there would seem to be much evidence that mild and many recurrent cases of thyrotoxicosis are so easily brought under control by thiouracil that use of the drug constitutes the best solution. Furthermore there are not a few cases of Graves' disease that because of circulatory or other complications represent far too great a risk to tempt the most courageous surgeon. For such thiouracil constitutes a boon and a new hope.

#### SUMMARY

1 Report has been made of 100 cases of thyrotoxicosis treated with thiouracil. Remission was induced in 87.

2 The drug exerted a beneficial influence on emaciation, tremor, hyperkinesia and circulatory symptoms, on basal metabolic rate, cholesterol levels and the creatine defect and on the tendency of thyrotoxic patients to lose nitrogen, calcium and phosphorus.

3 Studies of cholesterol levels and the extent of creatine defect were found to be valuable aids in following the effects of the drug

4 Protrusion of the eyeballs was not lessened but lid spasm, and lid lag were improved or controlled

5 Benefit from thiouracil was often apparent in less than 10 days and normal conditions were usually attained within 40 days Factors tending to retard the rate of response were previous use of iodine and large nodular goiters

6 Of the 100 cases, 73 were successful in the sense that they were maintained in remission In 37 of the 73 the drug was withdrawn for two to 16 and one-half months without relapse

7 The drug failed to excite favorable response in two, permitted relapse during treatment in four and exerted unsatisfactory control in two

8 There were three deaths from circulatory complications but none that could be justly ascribed to the action of the drug

9 In 12 cases, unfavorable symptoms resulted in withdrawal of drug In five of these there seemed to be little doubt that the untoward symptoms were caused by the drug

10 Two cases of agranulocytosis were encountered One was mild and transient, the other was severe and prolonged but recovered after seven days under the protective use of penicillin

11 Thiouracil is deserving of more extended and more general trial Evaluation of its rôle as an alternative to surgical treatment awaits further clinical experience

#### BIBLIOGRAPHY

- 1 ASTWOOD, E B Treatment of hyperthyroidism with thiourea and thiouracil, Jr Am Med Assoc, 1943, cxxii, 78
- 2 KENNEDY, T H Thioureas as goitrogenic substances, Nature, 1942, cl, 233
- 3 MACKENZIE, C J, and MACKENZIE, J B Effect of sulfonamides and thiourea on the thyroid gland and basal metabolism, Endocrinology, 1943, xxxii, 185
- 4 WILLIAMS, R H, and CLUTE, H M Thiouracil in the treatment of thyrotoxicosis, New England Jr Med, 1944, ccxxx, 657
- 5 SOLFY, M H Exophthalmos in patients with various types of goiter, Arch Int Med, 1942, lxx, 206
- 6 RICH, A R Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy, Bull Johns Hopkins Hosp, 1942, lxxi, 123
- 7 SLOAN, M H, and SHORR, E Metabolic effects of thiouracil in Graves' disease, Science, 1944, xciv, 305
- 8 ASTWOOD, E B Thiouracil treatment in hyperthyroidism, Jr Clin Endocrinol, 1944, iv, 229
- 9 GOLDSMITH, E D, GORDON, A S, and CHARIPPEN, H A An analysis of the effects of continued thiourea treatment in pregnancy and on the development of the offspring in the rat, Am Jr Obst and Gynec., 1945, xlix, 197
- 10 EATON, J C Treatment of thyrotoxicosis with thiouracil, Lancet, 1945, i, 171
- 11 PRESTON, J W, and THOMPSON, W O Persistence and recurrence of toxic goiter following subtotal thyroidectomy, Arch Int. Med, 1942, lxx, 1019

# HYPEROPHTHALMOPATHIC GRAVES' DISEASE\*

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My first job obviously must be to define, and defend, the somewhat monstrous title of my paper. The point is that an all inclusive term is needed to cover a spectrum of clinical pictures, probably of the same or similar etiology, which shade one into another. I have used the term Graves' disease for this purpose. Toxic goiter will not do because all the cases in the group are not toxic, nor do they all have goiters. Nor will exophthalmic goiter fill the bill for exophthalmos and related eye signs may be lacking.

Since the etiology of this disturbance is unknown, one is forced to resort to an eponym. Historically Parry is entitled to the honor, but Graves' name is more generally used and is more likely to be understood. It should also be recognized in naming the malady that it is by no means merely a thyroid disease. Rather is it to be looked upon as a widespread imbalance of some sort in which disorder of the thyroid is but one item. Other endocrines than the thyroid are involved, also the muscular, nervous, reticulo-endothelial, and lymphatic systems.

Now what of "hyperophthalmopathic"? The purpose here is to devise a term which will label adequately a subgroup within the general group covered by "Graves' disease," or, in other words, to define a variant from the more usual or classic picture of the malady. The cases in question are of course, those in which the ophthalmic phenomena overshadow the thyrotoxic, in which, indeed, thyrotoxicosis may actually be absent. My colleagues and I, being dissatisfied with any terms we could find in the literature, have been groping for some years for something better. "Hyperophthalmopathic" is the most recent result of this effort. It is distressingly polysyllabic but seems at least to be clear and accurate. Any case of Graves' disease may be "ophthalmic" or "ophthalmopathic," but the ones in question are unusually badly off as to their eyes—ergo, "hyperophthalmopathic." The term is intended to have no more separative connotation than black measles or galloping consumption. In viewing the whole spectrum of Graves' disease one sees at one end cases with thyrotoxicosis and no eye involvement and at the other (the hyperophthalmopathic) eye involvement and little or no thyrotoxicosis. In between these extremes there are all sorts of intermediate types. It should be further noted that the type may vary in the individual case. What starts off as classic may later come to fall within the hyperophthalmopathic category. It might be more accurate to say the hyperophthalmopathic *phase* of Graves' disease, rather than hyperophthalmopathic type.

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The hyperophthalmic phase is most frequently seen after thyroidectomy, and one concludes under these circumstances that thyroidectomy had something to do with initiating it, but it also may supervene in the patient without operation

It also should be stressed that the hyperophthalmopathic phase is relatively more frequent in males than females. To be sure, Graves' disease *in toto* is far more common in females, but among males with the disease, relatively more are in the hyperophthalmopathic phase than is the case in females

Surveying then the several phases, or types, of Graves' disease, one may recognize, among others, the following

Classic Graves' disease—that is to say, with ophthalmopathy, thyrotoxicosis and goiter

Graves' disease with thyrotoxicosis but no ophthalmopathy

Hyperophthalmopathic Graves' disease with—

(a) Hyperthyroidism

(b) Euthyroidism

(c) Hypothyroidism

Particularly interesting are the cases in which there is eye involvement and seemingly nothing else. In making diagnoses in cases falling within the area of Graves' disease, I favor, at present, either preceding that eponym with a suitable adjective as "classic" or "hyperophthalmopathic," or following it with a suitable descriptive phrase, such as "with severe thyrotoxicosis and minimal eye involvement." There may be added also "acute," "chronic," "fulminating," or "recurrent" as indicated. If one grades as to severity either ophthalmopathy or thyrotoxicosis from 0 to +++, then one may say that any of the following combinations may be found in naturally occurring Graves' disease \*

|  | Ophthalmopathy | Thyrotoxicosis |
|--|----------------|----------------|
| Classic Type or Phase                  | +              | +              |
|  | ++             | ++             |
|  | +++            | +++            |
| Graves' Disease without Ophthalmopathy | 0              | +              |
|  | 0              | ++             |
|  | 0              | +++            |
| Hyperophthalmopathic, Type or Phase    | +++            | 0              |
|  | +++            | +              |
|  | +++            | ++             |

From a classification point of view the eye signs themselves are very numerous. Our major concern is with their significance, and particularly whether there is more than one etiological type of ophthalmopathy in Graves'

\* In this connection it is interesting to go back to 1860 and note that Holthouse, discussing a case of C. H. Jones,<sup>1</sup> remarked that there are three kinds of Graves' disease, one in which the goiter and proptosis appear simultaneously, one in which the goiter preceded the proptosis, and a third in which the proptosis preceded the goiter. He believed the proptosis due to effusion of blood or serum into the orbit.

disease For practical convenience let us group the ophthalmic phenomena as follows

(a) *Those related to lid retraction*

Wide palpebral aperture

Lid lag

Staring or frightened expression

Exophthalmos (some believe the wide separation of lids per se permits protrusion of the globes)

(b) *Those related to extrinsic muscle weakness*

Limitation of movement of eyeball, especially upward

Diplopia

Exophthalmos (in part probably due to weakness of the recti)

(c) *Those due to swelling*

Exophthalmos (chiefly due to swelling of orbital contents)

Swelling of lids

Swelling of conjunctivae (chemosis)

As to the pathogenesis and etiology of the ophthalmopathy of Graves' disease there has been speculation for more than two centuries <sup>2, 3, 4, 5, 6, 7, 8, 9</sup> The evidence available indicates that swelling of the orbital contents is a very important, if not the sole, factor concerned in proptosis of the globes Weakness of the rectus muscles probably also plays a part, and the wide separation of the lids likewise is believed by some to be a factor

That lid retraction plays more than an adjuvant rôle seems to me very doubtful Considerable degrees of lid retraction may occur in Graves' disease without any proptosis <sup>10</sup> On the mechanism of lid retraction there is lack of agreement Pochin <sup>11</sup> considers it due to spasm of the levator palpebrae superioris, a striated muscle innervated by the oculomotor nerve, and he believes that sympathetic overactivity has nothing to do with it Mulvaney, <sup>12</sup> on the other hand, believes that lid retraction is due to spasm of Landstrom's muscle, a smooth muscle innervated by the sympathetic Landstrom himself believed this muscle to be the cause of proptosis also, although the muscle lies mainly in front of the globe

The evidence that swelling of the orbital contents is the major factor in exophthalmos is overwhelming The questions are, what is the nature of the swelling, and what causes it? Many investigators have considered edema of the entire orbital contents as chiefly responsible <sup>13, 14, 15, 16</sup> Others have thought that swelling of the extrinsic muscles played the chief part <sup>17, 18, 19, 20</sup> The recent series of papers by Rundle, Wilson and Pochin <sup>21, 22, 23, 24</sup> from the Westminster Hospital, London, make a strong argument for fat as the important item These investigators succeeded in obtaining complete dissections of the orbit at autopsy in 17 cases of Graves' disease and in 12 of them they were able to make exophthalmometric measurements, both ante and post mortem This is an astounding achievement It would be difficult in this country these days to gain access to such a mass of material



The chief point about the Westminster Hospital studies is that they show pretty conclusively that in the cases observed, orbital swelling was largely due to increase in fat. This increase in fat was quantitatively greatest in the orbital fibro-fatty tissue of the orbit, but was relatively greatest in muscles especially the levator palpebrae superioris, which is, they believe, responsible for the lid retraction. Rundle and Wilson<sup>23</sup> further give rather convincing evidence that the bulging of the lids so commonly seen in Graves' disease, and usually attributed to edema, is really due to deposits of fat. They point out that the swelling fails to pit on pressure as edema would, and instead is lumpy like fat. These fat deposits they believe due to a protrusion of fat from the orbit. If the muscles are strong and intraorbital pressure high, fat will ooze out about the eyeballs. Rundle and Wilson minimize the rôle of edema, and perhaps rightly, insofar as the cases they studied are concerned. They furthermore make the following comments "Hertz, Means and Williams"<sup>25</sup> "have developed the thesis that there are two different types of Graves' disease, the classical form and an 'ophthalmopathic form'. In the former there is exophthalmos and lid lag, in the latter, ophthalmoplegia and severe edema of the orbital and other tissues. But their theory is largely based on a false premise, namely, that edema of the orbital tissues is the proximate cause of the exophthalmos." The last statement of Rundle and Wilson is unjustified. Their series of cases, as far as one can judge from the rather scanty clinical data given, included none of what might properly be called malignant or progressive, exophthalmos, the type in which edema, at least of some of the structures concerned, is unmistakable. The conjunctivae in such cases are often edematous, and various surgeons doing decompression operations on the orbits, have reported edema of the orbital tissue. In the more malignant phases of the process swelling of the extrinsic muscles seems to be the chief factor involved in increasing the volume of orbital contents. Under these circumstances the increased bulk of the muscles appears to be chiefly due to increased water content and lymphocytic infiltration<sup>16, 20</sup>. Furthermore, regarding the question of accumulation of fat in the orbit versus that of water, it should be noted that a number of observers have mentioned the finding of edematous fat<sup>13, 20</sup>.

The precise cause of the swelling in the ophthalmopathy of Graves' disease has not been established with any degree of certainty. It is abundantly evident, however, that the anterior pituitary has something to do with it<sup>8, 12</sup>. Impressive exophthalmos has been produced in a wide range of vertebrate species by administration of anterior pituitary extracts, both in animals with thyroids intact, and in those which have been totally thyroidectomized.

Much point has been made in the literature of the great differences in the anatomy of the orbits in different species, and of the apparent differences in the mechanism of the exophthalmos. It is quite true that these differences exist. For example, Albert,<sup>27</sup> producing a very acute and marked type of exophthalmos by injections of anterior-pituitary extracts in the small fish *fundulus*, finds that the proptosis is caused by an effusion of fluid into

the orbit Upon withdrawal of this fluid the exophthalmos disappears Dobyns,<sup>28</sup> producing exophthalmos in guinea pigs, finds within a few hours of the administration of thyrotropic hormone, deposits of fat along the striations of the extrinsic muscle fibers of the orbit Later there is Zenker's degeneration of muscle fibers and edematous swelling of the muscle

In view of these differences it has been argued that the exophthalmos of animals has little or no bearing upon that found in human beings with Graves' disease But, contrariwise, it has also been assumed that because exophthalmos has been produced by anterior pituitary extracts in animals, the exophthalmos of Graves' disease is due to an excess of thyrotropin Neither of these conclusions is completely justified To my way of thinking it is very impressive that pituitary extracts produce exophthalmos in so divergent species as those of fish,<sup>27</sup> ducks<sup>29</sup> and guinea pigs<sup>30, 31, 32, 33, 34</sup> It is also impressive that many bits of evidence favor the view that there is hyperfunction of the anterior lobe in a human disease of which exophthalmos is a frequent manifestation But whether the anterior pituitary agent involved is identical with that which exercises the tropic action on the thyroid parenchyma, or something else which comes down in the same fraction, has not yet been determined

The muscular involvement in Graves' disease is very impressive It may involve the entire voluntary musculature, but usually produces its most conspicuous result in the eye muscles, because, as Pochin put it, during a recent visit to our clinic, "the orbit is the best tambour in the body" It would seem to be significant that the injections of pituitary extracts in animals produce changes both in the eye muscles and other skeletal muscles, that closely resemble those found in corresponding muscles in Graves' disease of man

The consequences of the ophthalmopathy of Graves' disease, when it enters what I have called the hyperophthalmopathic phase, exposure keratitis, corneal ulceration and scarring, ophthalmitis with perhaps the loss of one or both eyes, are sufficiently serious to make the solving of the problem of its pathogenesis one of great importance and urgency The lines of investigation which seem promising, some of which we are following, are first to identify the pituitary factor involved Is it thyrotropin or something related to it? Next to explore the mode of action of this agent on the tissues of the orbit, and factors which condition or inhibit its action There is considerable evidence that the action of thyroid hormone antagonizes that of thyrotropin, and there is also the possibility that other substances exist which are antihormonic with respect to thyrotropin The presence of an excess of fat in the orbit indicates, of course a thorough study of the entire metabolism of fat in Graves' disease and experimental exophthalmos in animals The ideal relief or cure of the condition will emerge from an understanding of the fundamental pathogenesis involved, and will supplant the type of therapy, largely symptomatic, which we are obliged to use at present

The remainder of my time I will devote to the practical problems of diagnosis and treatment

*In diagnosis* it is a question of recognizing the hyperophthalmopathic phase from the more classic phase. This, as I have tried to indicate earlier, is a matter of relative, not absolute, separation. The arguments of those who, like Mulvany,<sup>12</sup> believe that in hyperthyroidism there are two distinct types of exophthalmos, one of pituitary origin, one of some other origin, leave me unconvinced. Mulvany separates "thyrotoxic exophthalmos" from "thyrotrophic exophthalmos." These would correspond roughly to what I have called respectively the classic and hyperophthalmopathic types of Graves' disease. But whereas Mulvany considers these etiologically distinct, I incline to the view that they are not, agreeing in that respect rather with Rundle and Wilson.<sup>21</sup> The chief reason for my so believing is that all gradations of clinical picture between the extremes can be found, and that often in the same patient one will find at one time the classic picture, at another the hyperophthalmopathic. Mulvany's theories also are at variance with Rundle and Pochin's<sup>23</sup> facts. Mulvany, for example, states that there is no increase in bulk of orbital tissue in the "thyrotoxic" type of exophthalmos, which instead he believes due chiefly to weakness of ocular muscles, whereas in "thyrotrophic exophthalmos" increased bulk of orbital contents, due largely to swelling of the muscles, is the main factor. But Rundle and Pochin proved that there is increased volume of orbital contents in cases which seem clearly to belong to Mulvany's thyrotoxic type. It seems to me easy to believe that muscles which are swollen are also weak, and that most likely they were weak first, and later weak and swollen. What is really needed to settle these points is a method for measuring intraorbital pressure. At the present time Dr. David G. Cogan and I are making preliminary experiments with such an instrument. An efficient method for determining the titer of thyrotropin in the blood would also be of great value.

From the point of view of diagnosis then, as far as I am concerned, at the present time the problem is not one of distinguishing between etiologically distinct types but of deciding in any given case of Graves' disease whether the ophthalmopathy or the thyrotoxicosis constitutes the greater menace to the patient. How to recognize the cases in which the eyes are, or are likely later to make particular trouble, is what needs to be determined. As to the first, there is no real difficulty. That the eyes present a disquieting picture and that the thyrotoxicosis is slight or absent, is obvious. The manifestations which render the eye condition disquieting are chiefly those reflecting swelling and muscle involvement, namely, bulging of the lids, chemosis of the conjunctiva, limitation of ocular movements, and subjectively diplopia. These signs, in our experience, have more diagnostic significance with respect to the hyperophthalmopathic phase than do mere proptosis or the signs related to lid retraction. We have found, as have Rundle and Wilson,<sup>21</sup> that limitation of upward movement is the most impressive and probably the most significant of the muscle phenomena. It is

worthwhile to measure the eye movements in all directions from the straight forward axis. Rundle and Wilson<sup>35</sup> have devised an instrument for this purpose called the vertometer. We have found, however, that the ordinary ophthalmologic perimeter serves very well. With the patient's head stationary, he can be asked to follow with his eyes a flash light which is moved along the arc of the perimeter. When the corneal light reflex leaves the center of the pupil, the limit of movement has been reached, and the angle can be read off in degrees.

The measurement of intraorbital pressure will also be important when it can be quantitated. At present it can be only roughly approximated by palpation. One can get an impression of resiliency in the normal eye, or of doughy resistance in the hyperophthalmopathic eye of Graves' disease by pushing the eyeball back manually with the lids closed.

A much more difficult diagnostic problem is that of recognizing in advance cases in which the eyes are likely later on to enter the hyperophthalmopathic phase—this with a view to prophylaxis. Often of course it is impossible, but one or two suggestive points can be mentioned. For one thing, if the patient is a male, it should be recalled that he has a greater chance of going into the hyperophthalmopathic phase than would a female. The early occurrence of subjective ophthalmic symptoms should also suggest the possibility of an impending hyperophthalmopathic course. We have found, for example, that patients who show this type often consult the ophthalmologist first, because their eyes constitute their sole complaint, whereas those destined to run a classic course are apt to go directly to the physician for symptoms which can be attributed to thyrotoxicosis, and complain but little of eye symptoms. The early occurrence of chemosis and injection of the conjunctivae, and of epiphora are suggestive of the hyperophthalmopathic type, whereas marked lid retraction phenomena with little or none of the phenomena due primarily to swelling, favor the classic type.

*The treatment* of the hyperophthalmopathic type may be divided into specific and symptomatic.

Perhaps deserving of greatest emphasis is a specific, yet negative, form of therapy, namely, the avoidance of thyroidectomy in cases in which the development of a hyperophthalmopathic course is considered likely.<sup>36</sup> Certainly enough cases follow this course postoperatively to justify the belief that the removal of the thyroid played an important part in initiating it.

Patients in whom thyrotoxicosis is slight do not need thyroidectomy for their thyrotoxicosis, and it may aggravate their eye involvement. Under positive measures, more or less specific, we may mention the administration of thyroid, irradiation of the pituitary, and administration of substances antagonistic to thyrotropin.

The administration of thyroid is based, of course, on the theory that excess thyrotropic activity is a major factor, and that thyroid suppresses such action. I have given thyroid to tolerance in a large number of cases, and cannot say that it is productive of very immediate or dramatic improvement.

On the other hand, over a long period of time in many of the cases so treated, the ophthalmopathy at least ceases to progress, and in some there is slow improvement

Irradiation of the pituitary, in order to reduce its thyrotropic activity, we have tried in only one case. In that one rapid and impressive improvement occurred, but it may not have been due to the treatment. We have not used the method extensively because of fear of impairing other functions of the pituitary. Thompson and Thompson,<sup>37</sup> however, have used it in 38 cases of toxic goiter with fall in metabolism in 23. They do not state what the effects were on the condition of the eyes.

Antithyrotropic substances, for example, the serum of animals immunized against thyrotropin, might neutralize circulating TSH, and if the substance plays a part in the production of the ophthalmopathy, serve to counteract it. Lerman is working on the possibility but has no results to report as yet. The problem is to get a sufficiently pure thyrotropin.

In case of patients in whom ophthalmopathy and thyrotoxicosis are both severe, it is safer from the point of view of the ophthalmopathy to treat the thyrotoxicosis by one of the non-operative methods, e.g., by roentgen-ray or radioactive iodine. These, being slower in action, may be kinder to the eyes.<sup>38</sup> Drugs like thiouracil, in this regard, are probably to be classed with thyroidectomy. They produce what has been called a medical thyroidectomy, and are to be avoided for the same reasons as surgical thyroidectomy.

Symptomatic treatment of the ophthalmopathy is of several sorts. In the first place, the eyes must be adequately protected. Drying of the cornea with resultant exposure keratitis is the chief danger. Ulceration may follow and perforation. Greasing the eyes at bedtime with plain vaseline, and perhaps keeping the lids closed with tape or bandages may be indicated. Smoked glasses and goggles to keep dust out may also be useful in certain cases.

On the theory that edema of the orbital tissues plays a part, at least in some cases, we have used various depleting measures, for example, diuretics. The results have not been convincing. It is possible that some of the beneficial action of thyroid depends on its diuretic action, rather than on its pituitary inhibitory action. There is one locally depleting procedure which really seems effective. This is one which some of our patients discovered for themselves and told us about, namely, sleeping with the head elevated as much as possible. There seems definitely to be less swelling and feeling of tension in the eyes in the morning in the case of many patients who follow this practice.

Various measures have been aimed at improving the strength or reducing the swelling of the extrinsic muscles. We have, for example, used prostigmine in six cases with no observable benefit. Roentgen-ray treatment to the retrobulbar portion of the orbits has also been tried in a number of cases with questionable benefit in a few. The rationale of this therapy is

that the muscles are the seat of lymphocytic infiltration, which might be dispelled by roentgen-ray with consequent diminution in bulk, and perhaps improvement in muscle tone

Many surgical procedures from tarsorrhaphy to enucleation have been employed. They are indicated only when the eye is in danger. Tarsorrhaphy for corneal ulceration has sometimes been worth while, but the sutures are very apt to pull out. In marked chemosis, swollen conjunctiva has sometimes been resected. We have had no experience with this procedure in our own clinic.

Decompression by one of several available methods is the most important surgical procedure.<sup>30</sup> It should only be used in progressive exophthalmos when the integrity of the cornea is threatened. When vision is lost and the eyeball is in danger of infection, enucleation is indicated. This is the final operation of defeat.

In conclusion I will suggest that on the theoretical side studies of the action of pituitary extracts on the tissues of the orbit, of the rate of thyrotropin manufacture, of antithyrotropic substances, and of orbital fat metabolism are promising approaches to the underlying pathogenesis of the ophthalmopathy.

On the practical side I would urge that an attempt be made to recognize when patients with Graves' disease are in, or about to enter, the hyperophthalmopathic phase. This is important because the indications for treatment are different from those in the classic case. If recognized prior to thyroidectomy, this procedure should be avoided, and thyrotoxicosis, if it requires any treatment, should be treated by a non-surgical method.

Otherwise the treatment of the ophthalmopathy should be protective and possibly specific by means of thyroid. The surgical procedures should only be resorted to when cornea or eyeball is in danger.

It may be said in closing that in many instances over a period of months, or even years, there is a tendency to slow improvement, or at least cessation of progression, so that one can treat these cases conservatively and expectantly, provided they are kept under sufficient supervision to detect mischief before it becomes irreversible.

#### BIBLIOGRAPHY

- 1 JONES, C. H. On a case of proptosis, goitre, palpitation, *Lancet*, 1860, ii, 562.
- 2 DE SAINT-YVES, CHARLES. Nouveau traite des maladies des yeux, les remedes qui y conviennent, et les operations de chirurgie que leurs guerisons exigent. Avec de nouvelles decouvertes sur la structure de l'oeil, qui prouvent l'organe immediat de la vue, 1722. P-A Le Mercier, Paris.
- 3 COOPER, W. W. On protrusion of the eyes in connexion with anæmia, palpitation and goitre, *Lancet*, 1849, i, 551.
- 4 PONCET, A. In discussion of Gley on "De l'exophtalmie consecutive a la thyroïdectomie. Presentation d'un cas," *Compt rend Soc. de biol.*, 1910, lxxiii, 801.
- 5 KESSLI, L., LIPP, C. C., and HYMAN, H. T. Studies of exophthalmic goiter and involuntary nervous system. III. A study of 50 consecutive cases of exophthalmic goiter, *Arch. Int. Med.*, 1923, xxvii, 433.

- 6 PLUMMER, W A, and WILDER, R M Etiology of exophthalmos, constitutional factors with particular reference to exophthalmic goiter, *Arch Ophth*, 1935, xii, 833
- 7 GALLI-MAININI, C Exophthalmometric measurements in patients with thyroid diseases with some discussion of their significance, *Ann Int Med*, 1942, xvi, 415
- 8 MARINE, D Studies on the pathological physiology of the exophthalmos of Graves' disease, *Ann Int Med*, 1938, xii, 443
- 9 SEITCHIK, J N Mechanism of production of exophthalmos in exophthalmic goiter, *Arch Ophth*, 1942, xxvii, 762
- 10 EDEN, K C, and TROTTER, W R Lid-retraction in toxic diffuse goitre, *Lancet*, 1942, ii, 385
- 11 POCHIN, E E The mechanism of lid retraction in Graves' disease, *Clin Sci*, 1939, iv, 91
- 12 MULVANY, J. H The exophthalmos of hyperthyroidism, *Am Jr Ophth*, 1944, xx, 589, 693, 820
- 13 MOORE, R F Exophthalmos and limitation of the eye movements of Graves' disease, *Lancet*, 1920, ii, 701
- 14 THOMSON, E S Orbital edema in exophthalmic goitre, *Am Jr Ophth*, 1924, vii, 27
- 15 UNVERRICHT Experimentelle Untersuchungen uber die Ursache des Exophthalmus, *Klin Wchnschr*, 1925, iv, 878, and *Jr Am Med Assoc*, 1925, lxxxiv, 1969
- 16 KING, B T Cause of exophthalmos, *West Jr Surg*, 1931, xxxix, 602
- 17 NAFFZIGER, H C Progressive exophthalmos following thyroidectomy, its pathology and treatment, *Trans Am Surg Assoc*, 1931, xlix, 168
- 18 FRIEDENWALD, J S Orbital myositis and choked disc in exophthalmic goitre, *Ann Surg*, 1932, xcvi, 995
- 19 NAFFZIGER, H C Pathologic changes in orbit in progressive exophthalmos, with special reference to alterations in extra-ocular muscles and optic disks, *Arch Ophth*, 1933, ix, 1
- 20 SMELSER, G K A comparative study of experimental and clinical exophthalmos, *Am Jr Ophth*, 1937, x, 1189
- 21 RUNDLE, F F, and WILSON, C W Ophthalmoplegia in Graves' disease, *Clin Sci*, 1944, v, 17
- 22 RUNDLE, F F, and WILSON, C W Bulging of the eyelids with exophthalmos, *Clin Sci*, 1944, iv, 31
- 23 RUNDLE, F F, and POCHIN, E E The orbital tissues in thyrotoxicosis A quantitative analysis relating to exophthalmos, *Clin Sci*, 1944, v, 51
- 24 POCHIN, E E Exophthalmos in guinea pigs injected with pituitary extracts, *Clin Sci*, 1944, v, 75
- 25 MEANS, J H, HERTZ, S, and WILLIAMS, R H Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy, *Trans Assoc Am Phys*, 1941, lvi, 67
- 26 DUDGON, L S, and URQUHART, A L Lymphorrhages in the muscles in exophthalmic goitre, *Brain*, 1926, xlix, 182
- 27 ALBERT, A Personal communication, November, 1944
- 28 DONNAN, B M Personal Communication, March, 1945
- 29 SCHOENHART, J A Hyperplasia of the thyroid and exophthalmos from treatment with anterior pituitary in young ducks, *Proc Soc Exper Biol and Med*, 1931, xxix, 306
- 30 LOEB, L, and FRIEDMAN, H Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle, *Proc Soc Exper. Biol and Med*, 1932, xxx, 648
- 31 FRITHGOOD, H B Experimental exophthalmos and hyperthyroidism in guinea pigs Clinical course and pathology, *Bull Johns Hopkins Hosp*, 1934, liv, 48
- 32 SMELSER, G K Experimental production of exophthalmos resembling that found in Graves' disease, *Proc Soc Exper Biol and Med*, 1936, xxxv, 128
- 33 PALISSON, D L Experimental exophthalmos and muscle degeneration induced by thyrotropic hormone, *Proc Staff Meet Mayo Clin*, 1939, xiv, 828

- 34 AIRD, R B Experimental exophthalmos and associated myopathy induced by thyro-tropic extract, Arch Ophth, 1940, xxiv, 1167
- 35 RUNDLE, F F, and WILSON, C W Measurement of ductive movements of the eye, Clin Sci, 1942, iv, 385
- 36 MEANS, J H The nature of Graves' disease with special reference to its ophthalmic component, Am Jr Med Sci, 1944, ccvii, 1
- 37 THOMPSON, W O, and THOMPSON, P K Treatment of toxic goiter by irradiation of the pituitary, Jr Clin Invest, 1944, xxxiii, 951
- 38 SOLEY, M H Exophthalmos in patients with various types of goiter, Arch Int Med, 1942, lxx, 206
- 39 POPPEN, J L Exophthalmos, diagnosis and surgical treatment of intractable cases Am Jr Surg, 1944, lxxiv, 64



# THE EFFECTS OF THIOURACIL ON THE THYROID GLAND \*

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SINCE Plummer<sup>1</sup> instituted the use of iodine in the preoperative preparation of the thyrotoxic patient in 1923, little has been added to the management of thyroid disease except refinements of technic in the operative procedures. One of the most striking developments in the management of hyperthyroidism has come with the recent advances in chemotherapy. MacKenzie and MacKenzie,<sup>2</sup> in 1943, showed that sulphonamide treated animals developed goiters and hypometabolism. Astwood<sup>3</sup> sought a substance allied chemically to the sulphonamides which would be less toxic to human beings. After experimentation, he chose thiourea and thiouracil as the chemicals of least toxicity. He reported the clinical management of eight cases.

Since his report, thiouracil has been used almost entirely, and numerous articles, both clinical and experimental, have appeared in the literature. In most of these papers, the authors consider thiouracil, administered over a long period of time, as a substitute for surgery in the treatment of hyperthyroidism.

In this study, thiouracil has been used, not as a substitute for operation, but in the preparation of patients for operation as iodine is used and, therefore, the thiouracil has been administered over a relatively short period of time. In one exception, however, the drug was administered for seven months. A few examples, including this exception, have been chosen to illustrate the effects of thiouracil on the histology of the thyroid gland.

## CLINICAL AND HISTOLOGICAL DATA

*Thiouracil Preparation of a Thyrotoxic Patient* C G, a colored female, 31 years of age, was admitted to the Elizabeth Steel Magee Hospital on May 19, 1944 with the characteristic findings and symptoms of a diffuse toxic goiter of four months' duration. No iodine had been administered at any time and the basal metabolic rate on admission was +53 per cent. She was placed on thiouracil 0.2 gram, t i d, for a total dosage of 6.6 grams. The basal metabolic rate dropped to +16 per cent and subtotal thyroidectomy was performed ten days after starting the drug. There was only a moderate postoperative reaction. Forty-six grams of the gland were removed. It lacked the typical wet, vascular, friable appearance seen grossly in other thiouracil treated glands. Microscopically, this gland (figure 1) is one of the best examples of the changes induced by the drug. The acini are often without lumina and the ones with lumina contain a small amount of stringy, serum-like material. Occasionally, small compact particles of colloid are seen. The cells are tall, averaging 20 micra.

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high, with pale cytoplasm. The nuclei are vesicular and are toward the center of the cell, measuring as much as 10 micra in diameter. The picture is that of marked hyperplasia.

*Thiouracil Followed by Iodine Therapy in a Patient Who Developed Toxic Manifestations* E. M., a white female, 39 years of age, was admitted on June 4, 1944 with a severe, diffuse toxic goiter. Basal metabolic rate on admission was +49 per cent. There was a history of iodine administration one and a half years before admission,

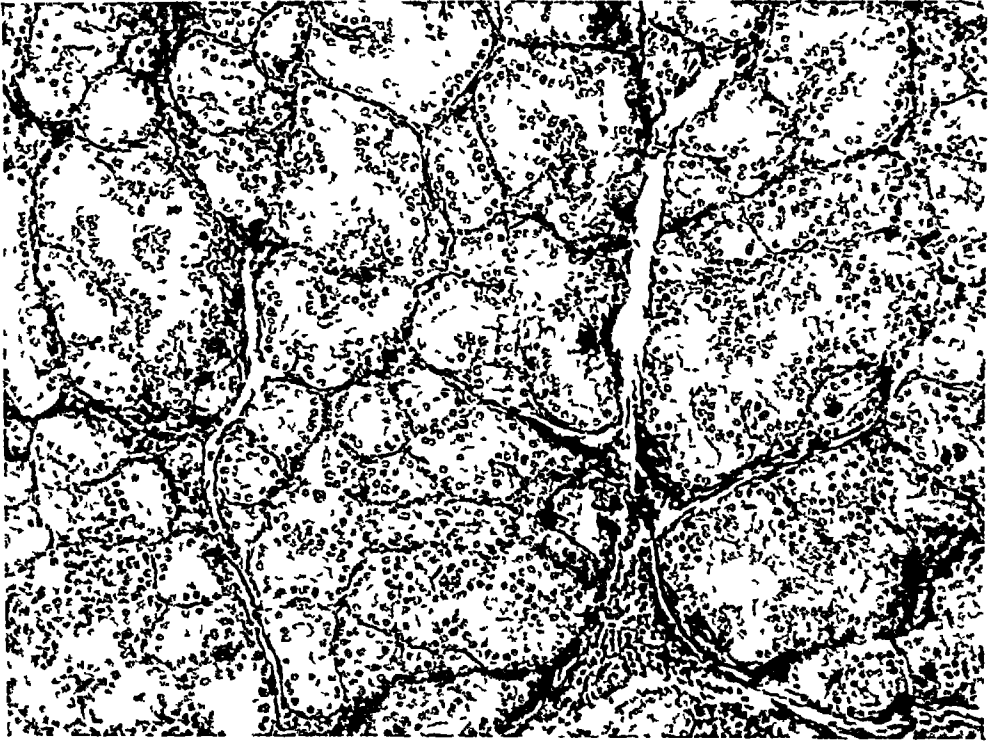


FIG 1 Thiouracil effect on a toxic goiter. The cells are tall and pale, the nuclei are large and toward the center of the cell. The acini are small and empty. Two small dark staining masses of inspissated colloid are seen.  $\times 135$

when the diagnosis was first made. No iodine therapy had been used immediately before admission. Thiouracil, 0.2 gram, t.i.d., was given for nine days for a total of 54 grams, when, because of an exacerbation of all the hyperthyroid symptoms associated with a diffuse macular rash, temperature elevation and nausea, the thiouracil was stopped. After a sharp drop in temperature and disappearance of the toxic symptoms, the drug was again started five days later. Almost immediately there was a return of the toxic symptoms, with temperature elevation, marked acceleration of pulse, excitement, nausea and the macular rash. Basal metabolic rate at this time was reported as +70 per cent. The drug was again stopped, and Lugol's solution was started min. XV, t.i.d. Four days later, the basal metabolic rate was +25 per cent. A subtotal thyroidectomy was performed eight days after stopping the thiouracil, and the gland removed was markedly vascular, very friable, and weighed 39 grams. Postoperative course was rather stormy, requiring secondary closing of the wound because of uncontrolled oozing from the cut surface of the gland. Microscopically (figure 2) most of the acini are distended with colloid which is separated from the cells in a droplet-like arrangement of clear spaces. The cells are not so tall as the cells in the thiouracil prepared gland and the nuclei are at the base of the cells.



FIG 2 This illustrates the involution in a toxic goiter after iodine preparation  $\times 115$



FIG 3 A very hyperplastic thyroid after iodine preparation  $\times 135$

The microscopic appearance of this gland is typical of the involution changes seen in toxic goiter after iodine therapy

*Comparison of Iodine Prepared Lobe and Thiouracil Prepared Lobe in the Same Patients* (1) V E Y, a white female, 25 years of age, was admitted on October 27, 1943 because of residual hyperthyroidism complicated by congenital heart disease. She had been operated upon in 1940 for an acute diffuse toxic goiter. Basal metabolic rate on the present admission was +18 per cent. Thiouracil, 0.2 gram, t.i.d., was given for 10 days, then increased to 0.2 gram five times daily. Operation was performed 28 days after thiouracil was started, a total of 24 grams having been given.

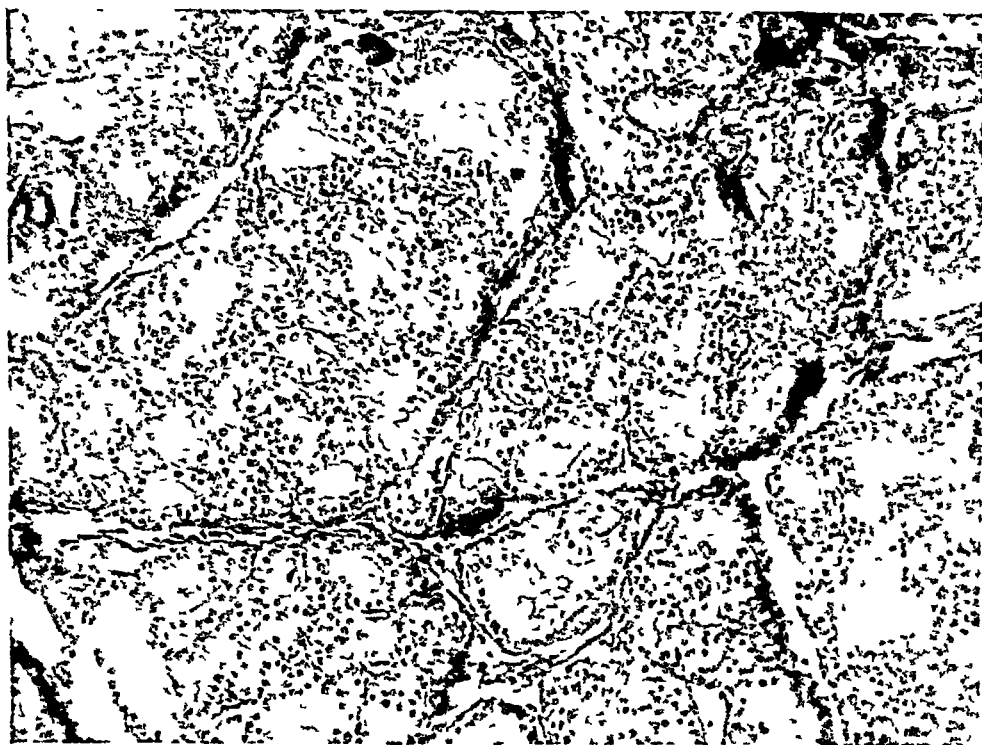


FIG 4 The appearance of the gland after thiouracil preparation. This lobe is from the same patient illustrated in figure 3, removed three years later because of residual hyperthyroidism.  $\times 135$

The thyroid tissue removed weighed 7 grams and was very friable and bled quite freely. Postoperative convalescence was uneventful. Basal metabolic rate on discharge from the hospital was +1 per cent. The gland prepared with iodine and removed in 1940 (figure 3) shows marked hyperplasia with acini containing a stringy granular colloid. The cells are tall and infolded with small nuclei toward the center of the cell. The portion of gland removed in 1943 following thiouracil preparation (figure 4) resembles the typical thiouracil prepared gland shown in figure 1 so closely that it is almost impossible to distinguish between them. Notice, again, the small acini, absence of colloid, tall cells, pale cytoplasm, nuclei in centers of the cells, and the small tight masses of colloid.

(2) H D, a white female aged 44, was first admitted on September 10, 1943 with a diagnosis of pericardial effusion and diffuse toxic goiter. Basal metabolic rates ranged from +60 per cent to +40 per cent. Operation was deferred because of the recent pericardial effusion. Patient was readmitted six months later at which time the basal metabolic rates were +84 per cent and +51 per cent. She was prepared

with Lugol's solution min XV, t i d, and a left lobectomy was performed 28 days later with a moderately severe reaction. Twenty-one grams of gland were removed. The patient was readmitted to the hospital for final lobectomy four months later. The basal metabolic rate was +35 per cent and the patient had regained 20 pounds in weight. She was placed on 0.1 gram of thiouracil, six times daily, for 16 days, receiving a total of 9.6 grams. At the second lobectomy 16 grams were removed. The tissue was pink, watery and friable and there was considerable oozing of blood at operation. Convalescence was complicated by a marked thermal response of 103° to 105° F in the first three postoperative days. The basal metabolic rate, on discharge, was -4 per cent, 11 days after final lobectomy.

The lobe removed after iodine preparation varied in its histological appearance. The area photographed (figure 5) shows hyperplastic acini distended with colloid.



FIG 5 A small area of toxic goiter after iodine therapy. The infolding and papillary arrangement are suggestive of tumor.  $\times 115$

The histology of the lobe removed after thiouracil preparation is even more variable than the iodine prepared lobe. It seems, at first glance, that the thiouracil had no effect on this gland and the appearance is not that of hyperplasia; in fact, the picture (figure 6) is that seen in simple colloid goiter. However, with further search, small patches of hyperplasia were found scattered through the gland and in these patches the characteristics of the thiouracil effect were seen.

*Thiouracil Therapy for Seven Months* B. M., a white male 67 years of age, was admitted in July 1943 with a diagnosis of diffuse toxic goiter and a left lobectomy was performed following preparation with Lugol's solution. Four months later, November 9, 1943, the patient was admitted again for lobectomy. Thiouracil, 0.2 gram, t i d, was started and increased to 0.2 gram five times daily, three days later, and further increased in another three days to 0.2 gram six times daily. A final

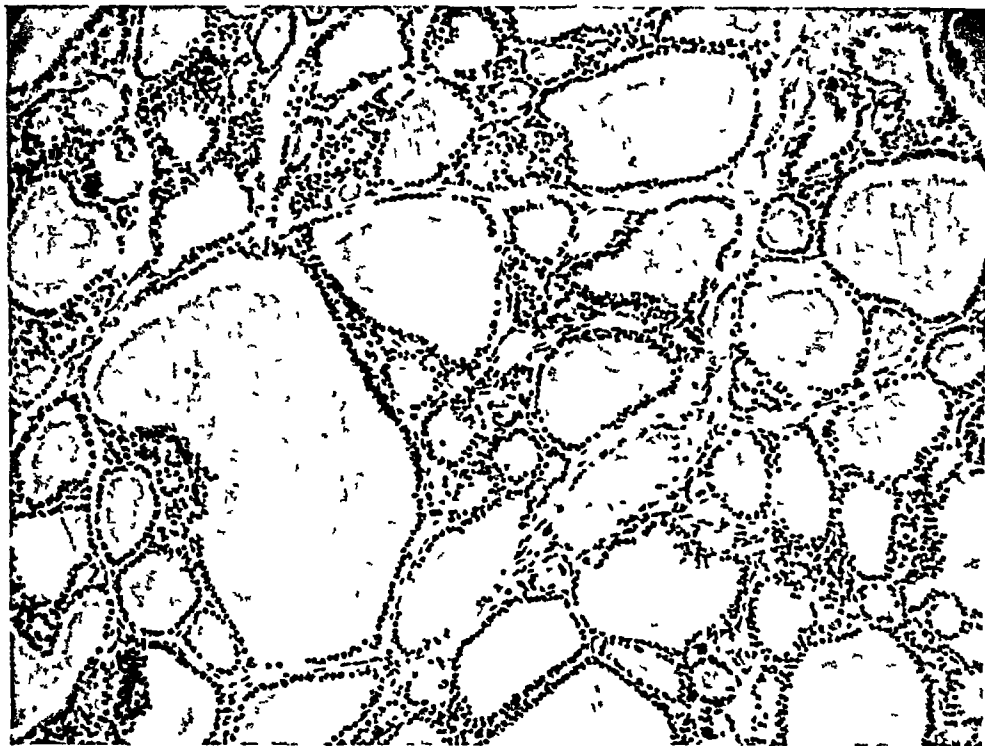


FIG 6 Simple colloid goiter unaffected by thiouracil  $\times 115$



FIG 7 Patchy architecture in an old toxic goiter after seven months of thiouracil therapy  $\times 135$

lobectomy was attempted one month later after a total dose of 28.8 grams of thiouracil had been given. The patient's condition became alarming after the initial skin incision was made and the operation was stopped. He was discharged from the hospital in four days on 0.2 gram of thiouracil, t.i.d. This medication was continued until readmission to the hospital seven months later because of persistence of his symptoms. Basal metabolic rate, however, was  $-3$  per cent and  $-4$  per cent on consecutive days. Final lobectomy was completed without difficulty three days after admission, and 36 grams of gland were removed. This patient had a total dosage of 135.0 grams of thiouracil over a period of seven months. Basal metabolic rate on discharge was  $+8$  per cent. In this case the microscopic appearance was at variance with the clinical

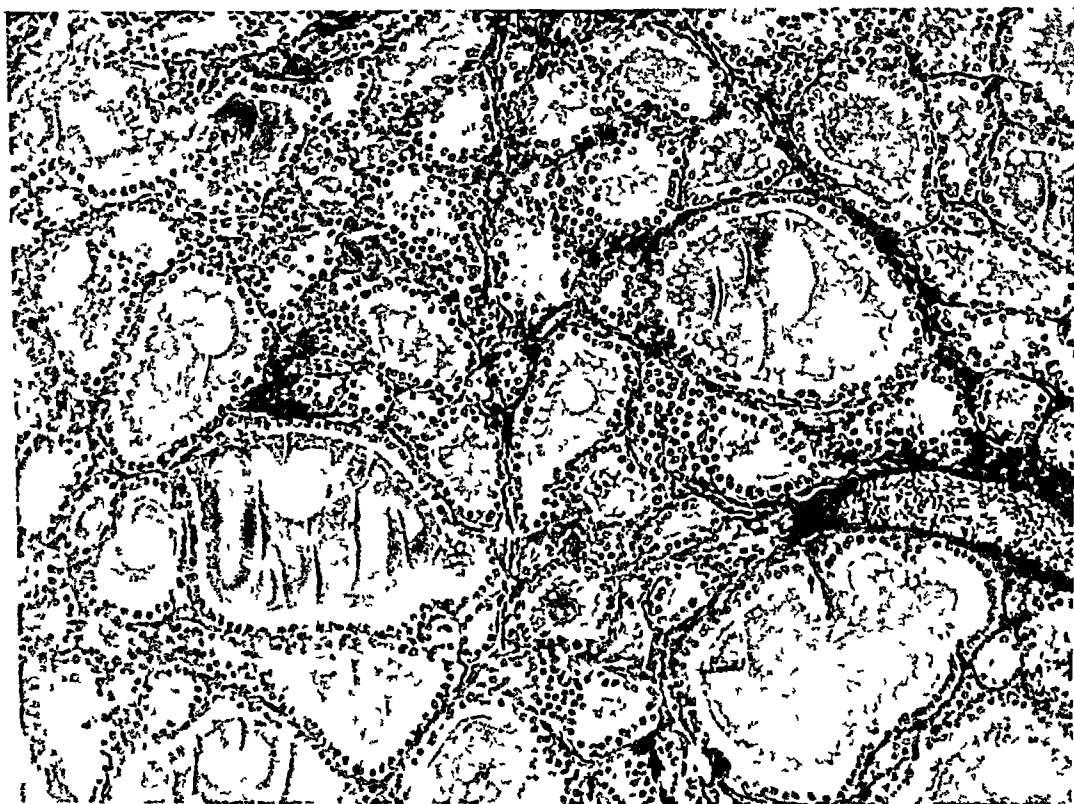


FIG 8 Toxic goiter resembling involution following iodine. This patient was treated with thiouracil for 19 days before thyroidectomy, but had been on iodine for many months before thiouracil was given.  $\times 135$

findings and, also, with the microscopic findings in other glands treated with thiouracil. Small and large acini are seen, none of them definitely hyperplastic (figure 7). Most of them contain colloid.

*Thiouracil Treated Gland in a Patient on Prolonged Iodine Therapy.* K. H., a white male 44 years of age, was admitted on November 14, 1943 with a diagnosis of recurrent diffuse toxic goiter. This patient had been operated upon by one of us (J. W. S.) in April 1937 for diffuse toxic goiter. He was quite well following the first operation, except at periods each year when he suffered from ragweed allergy (hay fever). Recurrence of the allergic condition required the administration of Lugol's solution in order to control loss of weight and tachycardia. The period immediately before admission, concurrent with his hay fever, was attended by marked exaggeration of his thyroid symptoms and enlargement of the gland itself. He had been taking iodine up until the time of his admission in the form of Lugol's solution min. V, t.i.d. with no benefit. Thiouracil, 0.2 gram, was administered five times

daily for seven days. The dose was increased to 0.2 gram six times daily for an additional 12 days. The total dose of thiouracil was 21.4 grams over a period of 19 days, after which subtotal thyroidectomy was performed. The basal metabolic rate was +28 per cent. At operation the gland was friable and bled freely, and 36 grams were removed. Postoperative course was stormy with a thermal response to 105.3° F., and secondary closure of the wound was necessary because of excessive oozing from the gland.

The iodine treated portion, removed in 1937, was extremely hyperplastic. The portion removed in 1943 illustrates the lack of thiouracil effect in a gland treated with iodine over a long period (figure 8). In fact, it can serve as a good example of an iodine treated toxic gland, with involution. The cells are moderately tall and most of the acini contain colloid. Comparison with figure 1 reveals the absence here of the hyperplasia seen in the typical thiouracil treated gland.

### DISCUSSION

Thiouracil, when not toxic to the individual, will control clinical hyperthyroidism in the operated as well as in the unoperated patient. In most cases, the thiouracil treated gland offers greater technical difficulties to the surgeon because of the increased vascularity and friability of the gland. In addition, the very toxic patient prepared for operation with thiouracil may have a stormy postoperative course, at times bordering on thyroid crisis.

The individual dosage and the length of time of administration have varied widely in the cases studied. It would appear that if thiouracil is to be used in preparation for operation, standards must be set up to determine when the patient is ready for operation. It is evident that the standards used for iodine prepared patients are not suitable for patients prepared with thiouracil. It is our opinion that iodine still is the drug of choice in the preparation of the thyrotoxic patient for operation.

Histologically, the human thyroid gland removed after preparation with thiouracil is markedly hyperplastic. It resembles closely the glands in experimental animals after administration of sulfaguanidine and thiourea as shown in the illustrations by MacKenzie and MacKenzie<sup>2</sup>. The cells are tall, have pale, finely granular cytoplasm with large nuclei occupying the center of the cells. The acini have small lumina and, at times, papillary infolding is seen. The colloid content is scarce, although some of the acini contain a thin stringy colloid. Occasionally, a small bit of deeply staining material is seen resembling inspissated colloid. Thin walled blood sinuses often traverse the gland. Degeneration sometimes occurs in areas where the cell outlines are distorted and the cytoplasm takes on a deeper stain. Small islands of lymphocytes may be seen. Lymph follicles are seldom seen although Means<sup>4</sup> and his group show such an example after 17 days of therapy.

Graham<sup>5</sup> pointed out that the thiouracil treated gland resembled the gland in hyperthyroidism before the use of iodine and stated further that the gland in endemic goiter also approximated the appearance of the thiouracil treated gland. Figure 9 is a photomicrograph of an untreated toxic goiter



removed in 1918. The hyperplasia is striking and the lumina contain very little colloid. The cells, however, are not as tall nor are they as granular as the cells in the thiouracil gland. Compare with figures 1 and 4.

The length of time the drug is used seems to affect the histologic appearance of the gland. In this series all but one were treated over a short period of time, 28 days or less, and the description of the thiouracil treated gland is based on the appearance of the gland tissue removed after a rela-

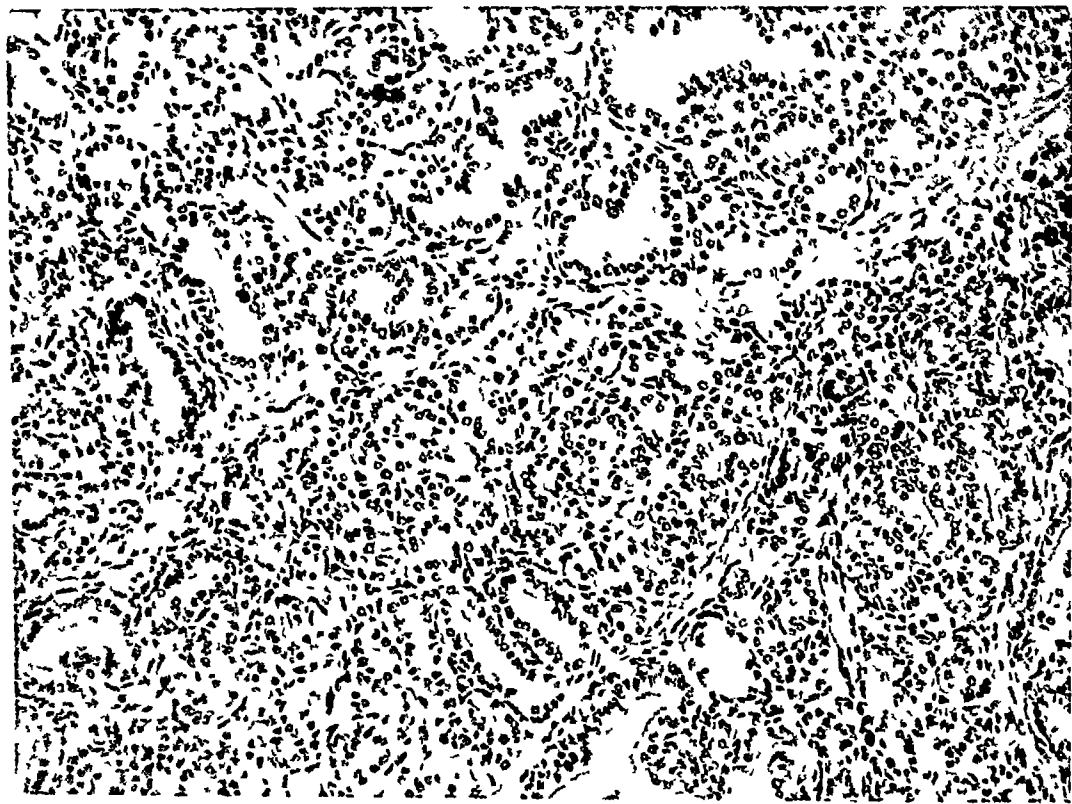


FIG. 9. Diffuse toxic goiter removed in 1918 before the days of iodine therapy.  $\times 135$

tively short time treatment. The one exception was a man treated for seven months and the appearance of the gland, figure 7, differs considerably. There are many acini widely distended with colloid, taking on the appearance of the gland undergoing involution. However, there are areas where the acini in small patches fit the description of the thiouracil treated gland.

The patchy distribution of the thiouracil effect may, at first glance, be confusing. In figure 6 there is no evidence of hyperplasia. The photomicrograph might well be that of a simple colloid goiter. Although most of the gland had this appearance, small scattered patches did show hyperplasia. It seems that the drug has little effect on the histology of colloid goiter and acts only on those portions of the gland that are hyperplastic at the beginning.

When iodine is given, following thiouracil, as in the case that developed toxic symptoms, illustrated by figure 2, the appearance approaches that of

the iodine prepared gland This patient received the drug for nine days followed by a five day rest period and eight days of Lugol's solution before thyroidectomy It might be said that thiouracil was not given over a long enough period Astwood<sup>3</sup> observed a latent period of one or two weeks before the effects of the drug were noticed On the other hand, figure 1 was made from the gland of a patient who was on thiouracil for 10 days only before thyroidectomy and the illustration is one of the best examples of thiouracil effect Therefore, in this case (figure 2) at least, iodine quickly overcame the changes produced by thiouracil

Similar masking is shown in the case of the man given thiouracil after prolonged iodine therapy Even though he was given thiouracil for 19 days, the appearance was still that of the iodine prepared gland (figure 8) and the thiouracil effect was not seen histologically

It is important in attempting to interpret confusing findings in thyroid pathology to remember that it is not always possible to correlate clinical and pathologic pictures This fact is ably discussed by Graham<sup>6</sup> and illustrated by a diagram at the end of his article

### SUMMARY

The thyroid gland removed after preparation with thiouracil is red, moist and friable and offers greater technical difficulties to the surgeon than the iodine prepared gland In some individuals, thiouracil is toxic Some very sick patients may have a stormy postoperative course Iodine, therefore, seems to be the drug of choice, thus far, in the preparation of thyrotoxic patients for operation

The histology of the thiouracil treated gland shows marked hyperplasia with tall pale cells and large nuclei toward the center of the cell Colloid is practically absent The picture resembles the histology of the toxic goiter before the days of iodine preparation Iodine administered either before or after thiouracil seems to mask the picture of hyperplasia seen when thiouracil is used alone

Thiouracil in this study was supplied through the generosity of the Lederle Laboratories, Inc, under the trade name "Deracil"

### BIBLIOGRAPHY

- 1 PLUMMER, H S Results of administering iodine to patients having exophthalmic goiter, *Jr Am Med Assoc*, 1923, **XXX**, 1955
- 2 MACKENZIE, C G, and MACKENZIE, J B Effects of sulfonamides and thiouracil on the thyroid gland and basal metabolism, *Endocrinology*, 1943, **XXXII**, 185-209
- 3 ASTWOOD, C B Treatment of hyperthyroidism with thiouracil and thiouracil, *Jr Am Med Assoc*, 1943, **CXXXII**, 78-81
- 4 MOORE, F D, SWENY, D N, COFF, O, RAWSON, R W, and MEANS, J H The use of thiouracil in the preparation of patients with hyperthyroidism for thyroidectomy, *Ann Surg*, 1944, **CXX**, 152-169
- 5 GRAHAM, A Personal communication
- 6 GRAHAM, A The thyroid gland in hyperthyroidism *Surg Clin N Am*, 1941, **XXI**, 1331-1363

# TREATMENT OF POSTPNEUMONIC THORACIC EMPYEMA WITH SULFONAMIDES, PENICILLIN AND REPEATED THORACENTESES \*

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THE principles to be considered in the treatment of pleural empyema are twofold, sterilization of the exudate within the pleural space and obliteration of this space by reexpansion of the lung. Where this can be accomplished without the development of dense pleural adhesions the early recovery of the patient without any permanent respiratory limitation is enhanced. In most standard treatises on the treatment of postpneumonic empyema thoracostomy, preferably with rib resection, is emphasized. Since Graham and the Empyema Commission<sup>1</sup> in 1918 demonstrated the importance of delaying operation until the pleural exudate had become thickened, open thoracostomy has been highly successful. Some disadvantages to thoracostomy, however, do exist. Osteomyelitis of a rib, delayed or incomplete reexpansion of the lung necessitating secondary operations either on the rib cage or in the nature of a decortication of the lung, pericarditis, broncho-pleural-cutaneous fistula and metastatic abscess are not infrequent complications and are the cause of a small but definite mortality rate. The principle of allowing the exudate to become thickened succeeded in lowering the high mortality rate attendant in operating upon postpneumonic empyema by awaiting the formation of adhesions. This prevented acute changes of pressure within the thorax which produced such occurrences as mediastinal shift and pulmonary edema. However, in allowing the exudate to become thickened and pleural adhesions to form, the seed was laid for the development of adhesions of the visceral pleura which in some instances precluded a proper reexpansion of the involved lung. Nevertheless, this principle in the surgical treatment of postpneumonic empyema proved to be sufficiently satisfactory for it to remain as the guiding dictum in the treatment of empyema up to this time.

Continuous closed intercostal suction or tidal drainage has been advocated and successfully used in numbers of instances. This procedure has certain definite disadvantages and there does not seem to be any real agreement on the technic or apparatus that is most effective<sup>2, 3, 4</sup>. Apparently it is most difficult to continue any type of closed intercostal drainage over a period longer than two or three weeks without leakage around the tube, development of secondary infection and pyopneumothorax and in a great many cases treated in this manner secondary rib resection was found to be necessary.

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The use of simple multiple aspirations offered little hope for cure, although it had been used occasionally with success,<sup>5</sup> until the advent of sulfonamides. With the use of these drugs to sterilize the pleural exudate repeated thoracenteses could then be utilized as a hopeful procedure. With the advent of penicillin another powerful antibiotic has been added to our armamentarium. By 1940 several cases treated with sulfonamides and multiple aspirations were reported in the literature, and in 1941 Keefer and his associates<sup>6</sup> in a study of hemolytic streptococcus pneumonia and empyema reported the recovery of four cases of streptococcus empyema by the use of sulfonamides and multiple thoracenteses without operation.

About this time it became evident to many surgeons and it was reported in the literature by Lanman and Heyl<sup>7</sup> and also by Burford and Blades<sup>8</sup> that in cases of pneumonia treated by sulfonamide therapy, in which the sulfonamides had been continued following the development of empyema, the pleural exudate was quite different in character from that seen in postpneumonic empyema observed before sulfonamide therapy came into use. Lanman and Heyl thought that the pus was thickened and more tenacious. Burford and Blades pointed out that the clinical course of the empyema was considerably modified, that the pleural exudate took a longer time to become sufficiently thickened to attempt surgical drainage, and that there was a tendency to multiple loculation within the pleural space. These latter surgeons thought it advisable to discontinue the use of sulfonamides when an empyema developed during the course of a pneumonia. These changes observed in the pleural exudate in empyema caused a certain amount of hesitancy and indecisiveness in the minds of a number of surgeons. Whereas in the past the proper point in the course of the disease to select for surgical intervention had been well recognized, some confusion as to the proper method of handling postpneumonic empyema in sulfonamide treated cases began to develop. Without any specific reference it appeared that some physicians thought that sterilization without complete evacuation of the pleural exudate was sufficient for a cure.

The purpose of this report is to relate the experiences and to draw certain conclusions incurred with the handling of 14 cases of postpneumonic pleural empyema. All cases were treated with sulfonamides and repeated thoracenteses, and in addition three cases received penicillin. During the year 1942 we began to receive in this general hospital a group of cases of postpneumonic empyema treated at various station hospitals in this Service Command. All of these cases had had sulfonamide therapy and one or more thoracenteses before admission here. Owing to the fact that these cases were treated in different hospitals and no standard method of therapy had been initiated, they presented varying clinical pictures. On admission to this hospital seven of these cases presented the picture of an empyema in which the pleural space had been sterilized but considerable exudate remained. In three cases no free exudate was present in the pleural space and only thickened pleura remained. None of these cases was acutely ill and

we determined to try the effect of repeated thoracenteses with the results as outlined in the following case reports. Early in the course of this period of time two cases of acute empyema were admitted from station hospitals and as our experience at that time was limited they were transferred to the surgical service for treatment. Later four cases of acute thoracic post-pneumonic empyema developed on our own service and were treated with available antibiotic drugs and repeated thoracenteses.

#### CASE REPORTS

*Case 1*, aged 22, developed lobar pneumonia on the left, was admitted to a station hospital April 11, 1942, and was placed on sulfathiazole therapy. On April 24 he developed an empyema on the left, and on April 29 about 300 cc of greenish, relatively thin fluid were aspirated. A short chain streptococcus was found on smear but did not grow out on culture. His temperature which had been elevated to about 102° F fell to below 100° F following thoracentesis. On May 1, 50 cc of exudate were aspirated. He was received at O'Reilly General Hospital May 14, and on May 22, 150 cc of thin fluid which was sterile on culture were removed by thoracentesis. By the first week in June he became completely afebrile, began to gain weight, and became ambulatory. By June 25 a roentgenogram showed only slight thickening of the pleura on that side. He was returned to limited duty because of previously existing bronchial asthma on November 23, 1942.

*Case 2*, aged 21, developed a lobar pneumonia on the left and was admitted to a station hospital March 17, 1942 where he was placed on sulfathiazole and later sulfadiazine therapy. About April 26 he developed an empyema on the left and on April 29, 300 cc of seropurulent fluid were removed by thoracentesis. Culture showed a nonhemolytic streptococcus. Following this thoracentesis his temperature fell from the level of about 102° F to below 100° F until May 7 when it rose to 103° F. He was transferred to O'Reilly General Hospital May 14, and on May 16, 375 cc of a yellow, somewhat thick seropurulent sterile fluid were aspirated. On May 19 his chest was again tapped and cloudy sterile fluid which was definitely thinner in character was removed. The temperature then fell to below 100° F, by June 13 the temperature returned to a normal level, and by June 26 he became ambulatory. A final roentgenogram taken September 3 showed only minimal pleural thickening, and he returned to full duty October 26, 1942.

*Case 3*, aged 37, developed scarlet fever March 17, 1942 and was admitted to a station hospital on that date. On March 26 he developed pneumonia in the left side and was placed on sulfathiazole therapy. On April 11 he developed pyrexia for 11 days and continued to run a low-grade fever following that. On June 1 a localized area of empyema was found and on June 9 a thoracentesis produced 150 cc of yellow pus which showed pneumococcus and staphylococcus on culture. On June 19 thoracentesis was done, and 150 cc of pus were evacuated. He continued to be febrile and on June 25 was received at O'Reilly General Hospital. Repeated thoracenteses were done, which yielded on June 29, 875 cc of sterile purulent fluid, July 3, 1,000 cc of sterile purulent fluid, July 9, 575 cc of sterile thin fluid, July 13, 14 cc of slightly thicker fluid and on July 15, 80 cc of a moderately thick fluid. Small amounts of saline were used to irrigate the pleural space on June 29 and July 3. By July 17 his temperature fell to below 100° F, became normal on July 27, and remained so. At this time he began to gain weight and shortly thereafter became ambulatory. A roentgenogram taken August 12 showed moderate pleural thickening and he returned to full duty November 6, 1942.

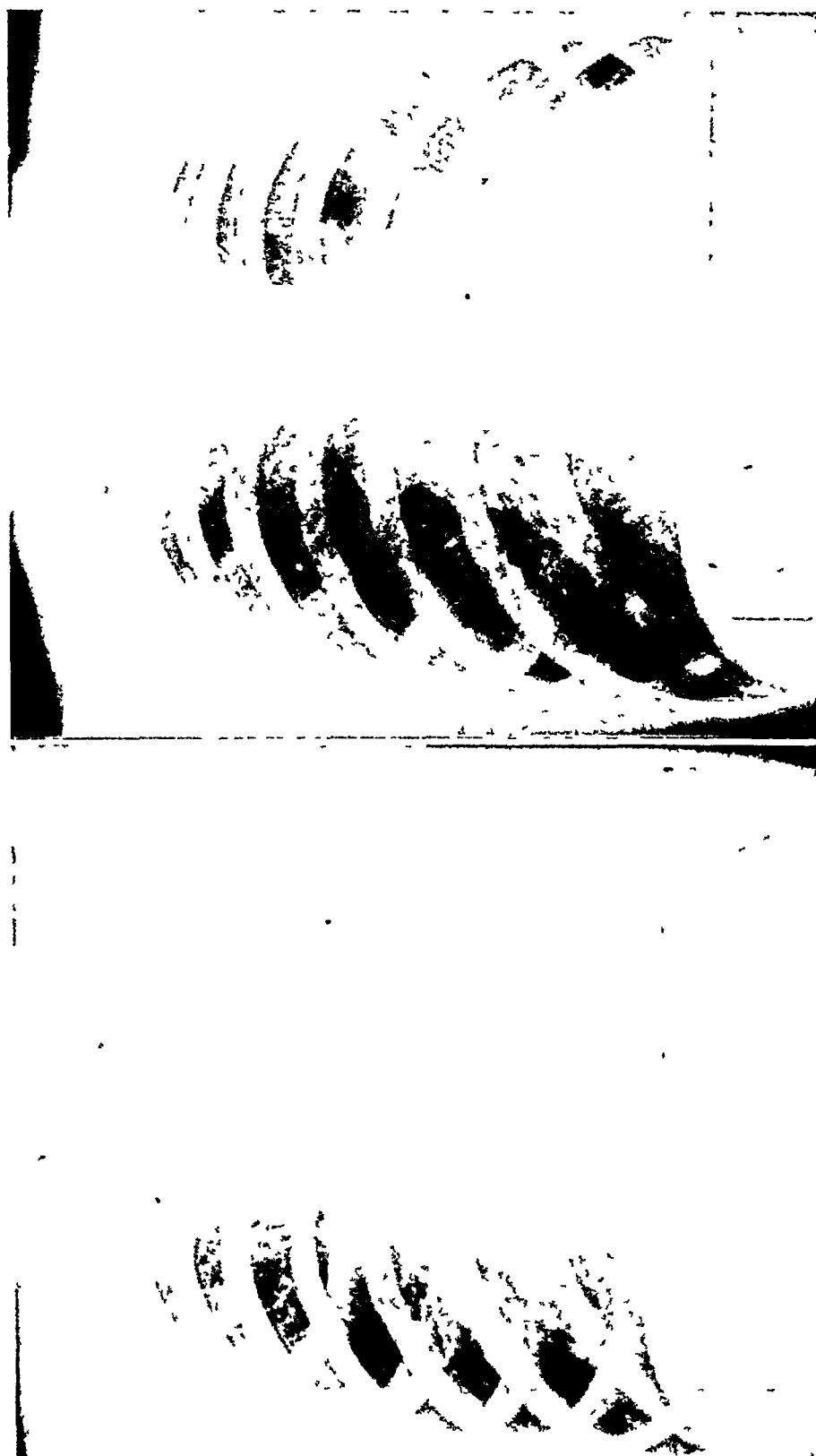


Fig. 1 Roentgenograms of case 3 (left, June 26, 1942, right, October 6, 1942) Onset of empyema about April 11, 1942 Five thoracenteses were done between June 26 and July 15, 1942 The last roentgenogram showed only a moderate degree of thickened pleura.

*Case 4*, aged 30, developed a lobar pneumonia on the right, was admitted to a station hospital on April 13, 1942 where he was placed on sulfathiazole therapy. On April 27 he developed an empyema on the right side and on April 30, 500 cc of a turbid fluid, which contained a beta hemolytic streptococcus and staphylococcus on culture, were removed by thoracentesis. On May 1, 850 cc and on May 5, 825 cc of a turbid seropurulent fluid were evacuated. On May 13, 600 cc of a thinner fluid were obtained by thoracentesis. Culture reports were not available for these latter three fluids. On June 9, 720 cc of a relatively thick, sterile, purulent fluid were aspirated. Again on June 12, 210 cc of a thinner fluid and on July 2, 350 cc of a seropurulent sterile fluid were obtained. The patient was acutely ill and had temperature as high as 103.8° F between April 27 and 30, following which his temperature fell to below 100° F, and after May 18 his temperature became normal and remained so. When he was received at O'Reilly General Hospital July 24, there was evidence of thickened pleura at the right base but no free fluid was found. He soon became ambulatory and began to gain weight. A roentgenogram taken December 12 showed only slight residual thickened pleura, and he returned to full duty December 31, 1942.

*Case 5*, aged 34, developed pneumonia and was admitted to a station hospital December 31, 1942. He was placed on sulfathiazole therapy which he received intermittently. Date of onset of the empyema could not be exactly determined, but on January 29, 1943, 75 cc of a seropurulent sterile fluid were obtained by thoracentesis from the left chest. Again on March 4, 100 cc of a similar fluid were obtained. The patient had intermittent fever as high as 101° F until February 6, 1943 when it fell and remained normal after February 10. He continued to have fluid in the chest and was admitted to O'Reilly General Hospital March 20, 1944. On April 5, 30 cc of a sterile rather thick fluid were evacuated by thoracentesis and on April 16, 75 cc of a similar fluid were obtained. The fluid on these two taps was rather thick and a small amount of saline was used to irrigate the pleural space. On April 21, 125 cc and April 23, 150 cc of a thinner sterile fluid were aspirated. During this period he remained afebrile and soon became ambulatory. By April 31 a roentgenogram showed only moderate pleural thickening and on June 6 this was minimal in amount. He was returned to limited service because of a polyglandular dysfunction on July 24, 1943.

*Case 6*, aged 25, developed an atypical pneumonia and was admitted to a station hospital January 25, 1943. The course of his illness was not serious until on February 1 he developed an empyema on the right and his temperature rose to 105° F. On February 3, 500 cc of a thin brown fluid containing 98,500 white blood cells per cu mm and a beta hemolytic streptococcus were evacuated. He was placed on sulfathiazole therapy on that date. On February 4, 500 cc of a thin seropurulent fluid were obtained and on February 5, 800 cc, February 6, 350 cc, February 7, 150 cc, and April 10, 100 cc of a thin sterile fluid were evacuated. This patient was very acutely ill at the onset of the empyema and had a stormy course with a bacteremia, a positive blood culture for beta hemolytic streptococcus on February 3 and February 4, acute nephritis and a severe anemia with hemoglobin of 33 per cent. However, following repeated thoracenteses his temperature fell to a lower level and patient began to show clinical improvement. In addition to the usual supportive therapy this patient received several transfusions. The patient continued to have fluid in the pleural space and was received at O'Reilly General Hospital May 1, 1943. On May 3, 150 cc of a thin brown sterile fluid containing 1950 cells of which 48 per cent were neutrophils were evacuated by thoracentesis. On May 5, 100 cc and on May 8, 130 cc of a similar fluid but containing only 180 white blood cells per cu mm were removed. Thoracenteses were continued, yielding May 12, 150 cc, May 15, 450 cc, May 17, 310 cc, May 21, 325 cc, May 27, 225 cc and June 4, 180 cc. Following these repeated thoracenteses of thin sterile fluid the patient showed further clinical

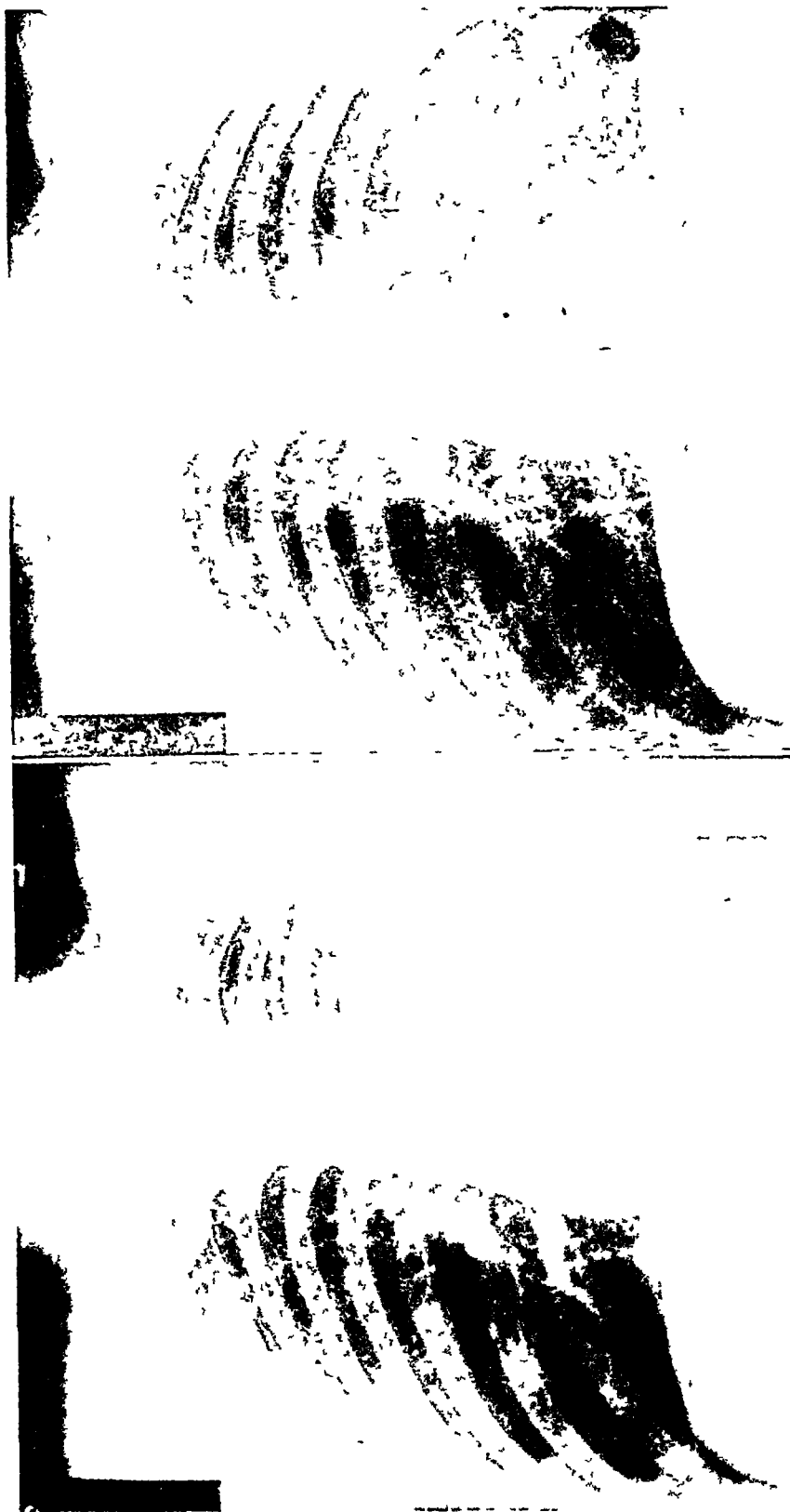


FIG. 2. Roentgenograms of case 5 (left, March 31, 1943, right, July 17, 1943). Onset of empyema about January 25, 1943. Four thoracenteses were done between April 5, 1943 and April 23, 1943. The last roentgenogram showed a minimal amount of pleural thickening.



improvement and by June 10 was afebrile, asymptomatic and ambulatory. Roentgenogram taken July 23 showed a moderate degree of residual thickened pleura. He returned to full duty August 6, 1943.

*Case 7*, aged 20, was admitted to a station hospital May 6, 1943 with what was apparently an acute upper respiratory infection and developed a lobar pneumonia on the left side on May 13, at which time sulfonamide therapy was begun. On May 18 he developed an empyema on the left. On May 25, 40 cc of a viscous sterile fluid containing 3,050 white blood cells per cu mm with 100 per cent neutrophils were evacuated by thoracentesis. His temperature which had been elevated to around 102° F promptly fell to 100° F. A considerable amount of fluid remained in the chest, but the patient remained relatively asymptomatic until in August his temperature again became elevated to as high as 102° F for a period of about a week. He was admitted to O'Reilly General Hospital August 26, 1943 and was placed on sulfadiazine therapy. On September 2, 450 cc of sterile seropurulent fluid were evacuated. On September 8, 450 cc and on September 19, 150 cc of a thinner sterile fluid were obtained. Shortly thereafter he became afebrile and ambulatory and on November 4 a roentgenogram showed only moderate pleural thickening. He was returned to temporary limited duty December 4, 1943 with the expectation that he would revert to full duty within a period of three months.

*Case 8*, aged 35, was admitted to a station hospital December 27, 1943 with what was apparently an acute upper respiratory infection, and developed an atypical pneumonia January 19, 1944. He received sulfonamides intermittently and on February 4, 1944 he developed an empyema on the right and had an intermittent elevation of temperature as high as 102° F, but usually below 100° F. On March 9, 20 cc of a thick green pus containing a type XII pneumococcus was evacuated by thoracentesis from the right chest. The temperature returned to normal and on March 23 he was received at O'Reilly General Hospital at which time he was afebrile and ambulatory. Examination demonstrated that there was no free fluid present in the chest but only some thickening of the pleura which showed considerable clearing by roentgenogram on April 28. He was returned to limited duty on May 17, 1944 with the expectation that he would revert to full duty within a period of three months.

*Case 9*, aged 18, developed scarlet fever and was admitted to a station hospital January 10, 1944. During the course of scarlet fever he developed bilateral bronchopneumonia for which sulfonamide was prescribed, but on January 19 he developed empyema in the left chest. On January 20, 650 cc of seropurulent fluid with specific gravity of 1.020, showing beta hemolytic streptococcus on culture, were evacuated by thoracentesis. On January 22, 360 cc, January 23, 690 cc, January 26, 120 cc of sterile fluid were aspirated. Following initial thoracentesis the temperature dropped to 100° F or below, and by February 9 it became normal. He was received at O'Reilly General Hospital March 30, 1944. Examination at that time showed only a slight amount of thickened pleura and he was placed on an ambulatory regimen and returned to full duty May 9, 1944.

*Case 10*, aged 19 developed atypical pneumonia and was admitted to a station hospital February 6, 1944. On February 25 he developed an empyema on the left and was started on sulfadiazine which was continued until March 4. On February 28, 500 cc of turbid fluid which showed a beta hemolytic streptococcus on culture were evacuated by aspiration from the left chest. On March 1 he was started on penicillin intramuscularly and continued until March 15. On March 2 a small amount of turbid fluid containing beta hemolytic streptococcus was aspirated and 10,000 Oxford units of penicillin were injected into the left pleural space. On March 5 and on March 7 unspecified amounts of sterile fluid were evacuated from the left chest. Following this latter aspiration his temperature fell to below 100° F, and became normal after March 16. This patient was very acutely ill for about a week and in addition to the



FIG. 3. Roentgenograms of case 12 (left, November 13, 1944, right, November 30, 1944). Onset of empyema November 10, 1944. Four thoracenteses were done between November 13 and November 16, 1944. The last roentgenogram showed minimal amount of pleural thickening.



FIG 4 Roentgenograms of case 13 (left, April 17, 1945, right, May 15, 1945) Onset of streptococcus bronchopneumonia and empyema on the left on April 16, 1945 The shadow on the left side in the roentgenogram of May 15, 1945 represents pleural thickening only

usual supportive treatment he received three blood transfusions. He was received at O'Reilly General Hospital April 3, 1944 at which time he was ambulatory and afebrile, and roentgenogram of the chest showed only minimal amount of pleural thickening. He returned to full duty May 30, 1944.

Case 11, aged 21, was admitted to O'Reilly General Hospital from the command March 28, 1944 with atypical pneumonia. He was placed on sulfadiazine therapy,

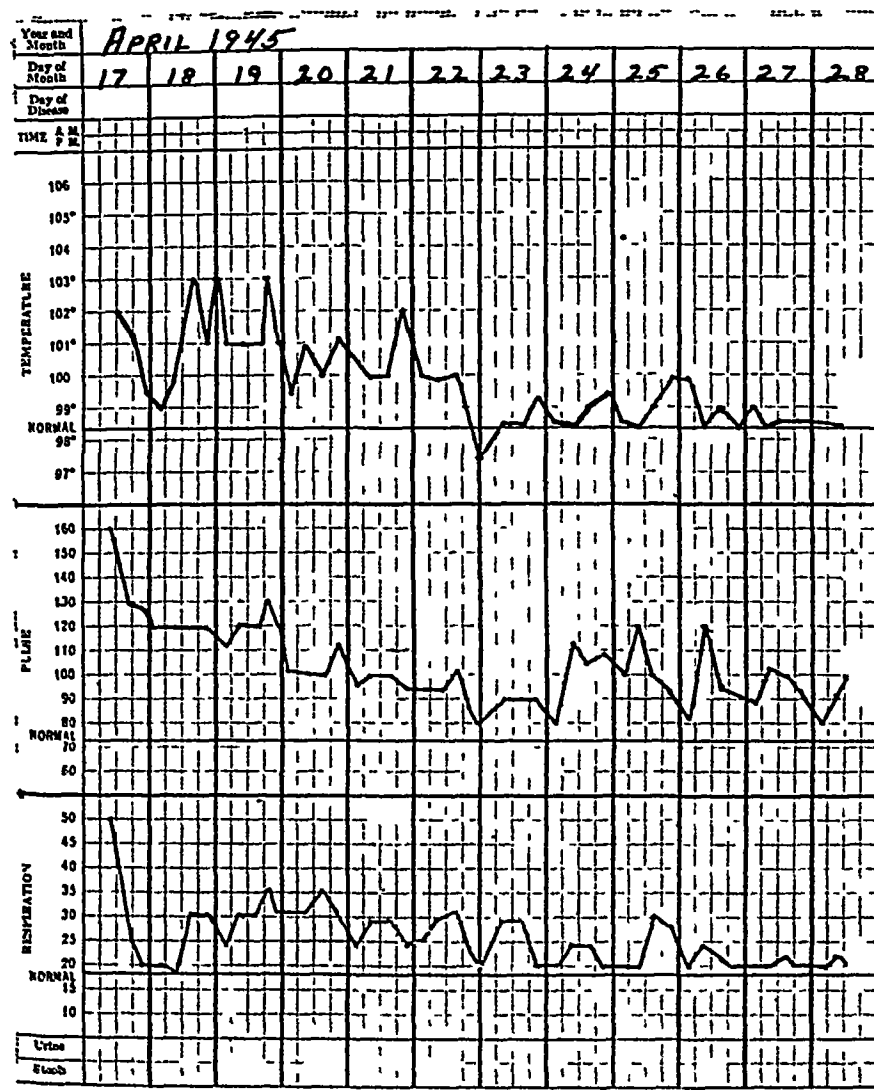


FIG 5 Temperature curve of case 13 Onset of empyema April 16, 1945

but on April 2 he developed an empyema on the left side. On April 4, 75 cc of sterile seropurulent fluid containing 6,400 white blood cells per cu mm were evacuated from the left chest. On April 8, 20 cc of a thinner sterile fluid were aspirated, and the temperature returned to a normal level. He became ambulatory, and on April 14 a roentgenogram of the chest showed only minimal pleural thickening which cleared almost entirely by April 21, and he returned to duty April 30, 1944.

Case 12, aged 25, a sailor on furlough was admitted October 9, 1944 to O'Reilly General Hospital with type II pneumonia of the left lower lobe. He was placed on

sulfadiazine for five days and his temperature returned to normal level within 24 hours, but there was a slow resolution of the pneumonic process On November 10, 1944 he developed an empyema on the left side and sulfonamide therapy was again started On November 13, 800 cc of a cloudy sterile seropurulent fluid containing 5,600 white blood cells per cu mm and having a specific gravity of 1.023 were obtained by thoracentesis from the left chest On November 14, 750 cc, November 15, 500

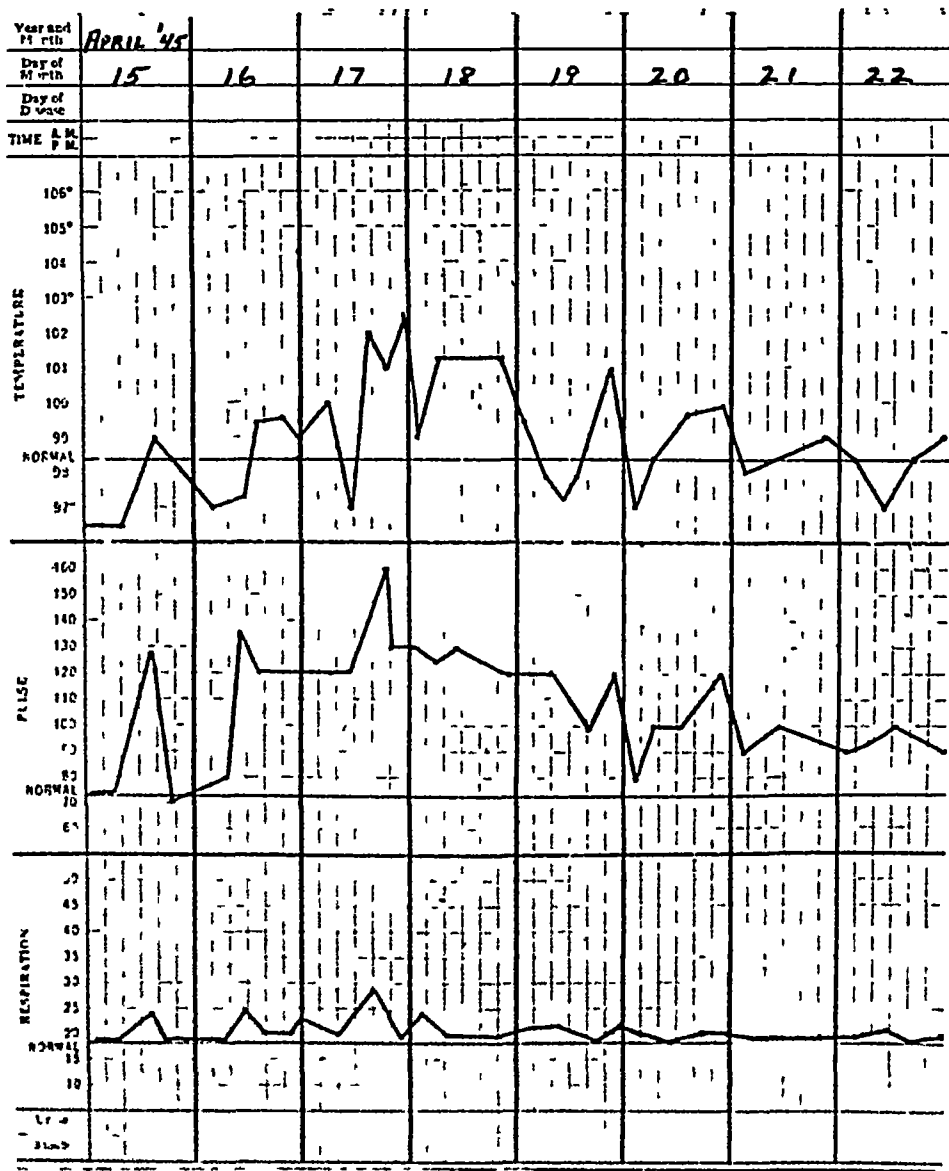


FIG. 6 Temperature curve of case 14 Onset of empyema April 17, 1945 Temperature remained normal after April 22, 1945

cc, November 16, 250 cc, of thin, cloudy, sterile fluid were aspirated His temperature was elevated only slightly for three days with the empyema He was never acutely ill, he became ambulatory about December 1, 1944 and returned to a furlough status December 8, 1944

Case 13, aged 19, developed scarlet fever while on furlough on April 10, 1945 and was placed on small doses of sulfadiazine On April 16 he became acutely ill with symptoms of acute pulmonary infection and was admitted to O'Reilly General

Hospital April 17 On admission he was severely ill with temperature 102° F, pulse 160, respirations 50, deep cyanosis and considerable dehydration He was found to have bilateral bronchopneumonia and empyema on the left and was immediately placed in an oxygen tent Intravenous sulfadiazine and intramuscular penicillin therapy were initiated A thoracentesis was promptly done and 1,000 c c of a turbid brownish fluid with specific gravity of 1.022 were obtained This fluid contained 13,750 white blood cells per cu mm with 99 per cent neutrophils and beta hemolytic streptococcus was found on culture Forty thousand units of penicillin were instilled into the pleural space On April 18, 250 c c of a lighter colored sterile fluid with specific gravity of 1.020 and containing 11,000 white blood cells per cu mm were obtained, and again 40,000 units of penicillin were instilled into the pleural cavity Further thoracenteses were done with the following results April 20, less than 10 c c, April 23, 160 c c of a thin sterile fluid with specific gravity of 1.015 and 3,300 white blood cells per cu mm, April 28, 35 c c of brown sterile fluid with specific gravity of 1.022, April 30, 30 c c, May 4, 40 c c, May 10, 30 c c The fluid obtained on the last three taps contained some blood and increased numbers of white blood cells and the specific gravity was as high as 1.030 Promptly following the first thoracentesis there was marked clinical improvement with considerable clearing of the cyanosis and reduction of the temperature, pulse and respiratory rate By April 22 the temperature fell to below 100° F, the patient began to regain his appetite and strength, and by April 29 the temperature fell to normal Penicillin was discontinued and he was allowed out of bed on May 9 Sulfadiazine was continued until May 15 On May 15 roentgenogram of the chest showed only moderate residual pleural thickening on the left On May 18 temperature rose to 103° F for 12 hours and the patient had what was probably a mild recrudescence of the pneumonia Sulfadiazine was again given, and he became asymptomatic after 48 hours

*Case 14*, aged 27, was originally admitted to this general hospital March 10, 1945 because of repeated attacks of left hemiparesis The neurological service determined that he had an intracerebral aneurysm, and ligation of the right common carotid artery was done March 29 Three days later he developed pneumonia at the right base with later involvement of the left lower lobe He was placed on sulfonamide therapy and on April 11 intramuscular penicillin therapy was begun On April 18 he developed an empyema on the right and on April 19, 450 c c of sterile sero-sanguineous fluid were aspirated This fluid contained 8,350 white blood cells with 85 per cent neutrophils per cu mm, and had a specific gravity of 1.018 On April 19, 450 c c of a similar sterile fluid were aspirated, April 21, 600 c c of a similar fluid containing 2,250 white blood cells per cu mm, April 22, 600 c c of a similar fluid, and on April 23 a thinner fluid containing practically no white blood cells was obtained by thoracentesis Further attempts at aspiration failed to produce any fluid On April 20 the patient's temperature fell to below 100° F, and by April 29 it became normal Penicillin was continued until May 8 and sulfadiazine continued until May 14 On May 11 roentgenogram showed evidence of a moderate amount of thickened pleura and an elevated diaphragm on the right side By May 15 the patient was asymptomatic as far as the chest was concerned and was transferred back to the care of the neurosurgical service

## DISCUSSION

It appears from our experience that postpneumonic empyema, when the infecting organism is a pneumococcus, staphylococcus or streptococcus, can be successfully treated by the use of sulfonamides, penicillin and repeated thoracenteses Sulfonamides alone when given by mouth or intravenously

tions Our experience with penicillin has been limited to three cases (10, 13, 14), but in one case (10) the pleural exudate was not sterilized after five days on sulfonamide and rapidly became sterile after intrapleural injection of penicillin It certainly appears that it would be advisable, where the effecting organism is suspected of being penicillin sensitive, to instill that drug into the pleural space until the exudate becomes sterile Whether further injections are advisable may be questionable, as it is possible that the drug may have an irritating effect on the pleura as it apparently does on the meninges<sup>9</sup> In none of our cases was sulfonamide used locally It is most important that the initial thoracentesis be done early in the course of empyema whether the disease accompanies or follows the preceding pneumonia Every attempt should be made completely to evacuate the pleural space initially as far as practicable Amounts up to 1000 cc can be removed with safety, but generally if the taps are done promptly considerably less fluid will be obtained Thoracentesis with complete evacuation of the exudate should be repeated at frequent intervals of one or more days as the exudate reforms and should be continued until no further fluid is found. Complete examination, including smear, culture, cell count and specific gravity, should be made on each specimen Although small amounts of sterile serous fluid may be reabsorbed, the removal of all such fluid as far as practicable enhances the convalescence of the patient and decreases the formation of pleural adhesions All means available should be used accurately to locate any pleural exudate Careful physical examination, roentgenograms with the usual technic and the Potter-Bucky technic, fluoroscopic examination and exploratory aspirations all have their usage Thoracentesis should be done with the usual precautions by a closed method Replacement of removed fluid with air was not done in our cases, but on several occasions small amounts of air inadvertently escaped into the pleural space without any deleterious results Where small amounts of thin fluid remain in the pleural space the careful injection of about 25 cc of air may be of aid in localizing any remaining fluid

Admitting that 14 cases is a small series upon which to base any definite conclusions, the course of these cases, and others reported in the literature, has led us to the belief that a procedure different from the generally accepted surgical method of handling postpneumonic empyema should be considered In addition to the four cases reported by Keefer and his associates,<sup>8</sup> Blades and his co-workers<sup>10</sup> in a recent report of 24 cases of thoracic empyema found that three cases were apparently cured by the use of repeated thoracenteses without thoracostomy These latter authors were of the opinion that if thoracenteses had been more assiduously employed a greater number of their cases would have recovered without operation Our recommendation is that postpneumonic empyema caused by organisms susceptible to sulfonamide and penicillin therapy should be treated by the continued use of these drugs and early and frequently repeated thoracenteses until no further

exudate is present in the pleural space. The exudate should not be allowed to form thick pus. Where such procedures can be successfully carried out thoracostomy should not be necessary. In certain instances the pleural exudate may be encapsulated in an area which precludes safe and adequate drainage by thoracentesis and in such cases the surgical approach would be necessary.

### SUMMARY

1 Fourteen cases of postpneumonic thoracic empyema were successfully treated without complication by the use of sulfonamides, penicillin and multiple thoracenteses.

2 When thoracentesis was done early in the course of the empyema and was frequently repeated the pleural exudate, which was rapidly sterilized, became less purulent and more serous in character and could be completely evacuated.

3 From these clinical observations we feel that this method should be routinely applied in postpneumonic empyema. The previously accepted procedure of allowing the pleural exudate to become thickened and performing a thoracostomy should be applied only when thoracentesis cannot be safely used because of the location of the exudate or where the infecting organism is resistant to sulfonamides and penicillin.

### BIBLIOGRAPHY

- 1 Empyema Commission. Cases of empyema at Camp Lee, Va., Jr. Am. Med. Assoc., 1918, lxxxi, 366.
- 2 HART, D. Acute empyema. Treatment by tidal irrigation and suction, Arch. Surg., 1929, xix, 1732.
- 3 WANGENSTEEN, O. H. Observations on the treatment of empyema with special reference to drainage and expansion of the lung, Jr. Thorac. Surg., 1935, iv, 399.
- 4 POTH, E. J., and MATHES, M. E. The treatment of acute empyema by continuous tidal drainage, Surgery, 1943, xiv, 617.
- 5 GRAHAM, E. A., SUIGER, J. J., and BALLOU, H. C. Surgical diseases of the chest, 1935, Lea and Febiger, Philadelphia.
- 6 KEEFER, C. S., RANTZ, L. A., and RAMMEIKAMP, C. H. Hemolytic streptococcal pneumonia and empyema, a study of 55 cases with special reference to treatment, Ann. Int. Med., 1941, xiv, 1533.
- 7 LANMAN, T. H., and HYAL, H. H. Empyema in children, New England Jr. Med., 1939, cxxxi, 1003.
- 8 BURFORD, T. H., and BLADES, B. Influence of sulfonamide therapy on postpneumonic empyema thoracis, Jr. Am. Med. Assoc., 1942, cxviii, 950.
- 9 PITCHER, C., and MEACHAM, W. F. The chemotherapy of intracranial infections, Jr. Am. Med. Assoc., 1943, cxviii, 330.
- JOHNSON, H. C., and WALKER, A. E. Intraventricular penicillin, Jr. Am. Med. Assoc., 1945, cxviii, 217.
- 10 BLADES, B., HAMILTON, J. E., and DUGAN, D. J. Observations on the treatment of empyema thoracis with penicillin, Surgery, 1945, xvii, 572.



# THE EARLY DIAGNOSIS OF FILARIASIS AND CERTAIN SUGGESTIONS RELATIVE TO CAUSE OF SYMPTOMS\*

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FILARIASIS has long been characterized by the physical findings of elephantiasis, lymphadenitis, marked physical deformity, and by the demonstration of microfilariae on blood smear. These features are indicative of a "late stage" of filariasis. The military necessity for occupation of filarial endemic areas has afforded an opportunity to study the "early stages" of filariasis. The syndrome of early filariasis has been outlined by Wartman and King,<sup>1</sup> and by various medical officers who have recently returned from the area in which filariasis is endemic. Since September of 1943, we have had an opportunity to study the "early stages" of filariasis. All patients included in this survey came from islands in the South Pacific areas on which filariasis was known to be endemic both from a clinical examination of the natives and by demonstration of microfilariae in the blood smear of these natives. It will be shown that by careful review of symptoms, physical examination, and laboratory findings, it is possible to make a definite diagnosis of filariasis prior to the development of the formerly accepted criteria for this diagnosis.

The patients considered in this study are a group of 100 soldiers evacuated from widely separated areas in the Southwest Pacific. The average age of the group was 26.6 years. The average time spent in endemic areas prior to the development of symptoms of filariasis was 13.3 months. The number of months from the time of entry into the endemic areas to our observation was 16.3 months. Our period of observation averaged 7.3 weeks.

In establishing the diagnosis of filariasis, the following factors were considered: (1) The residence and length of stay in areas where filariasis is known to be present; (2) the history of symptoms associated with the early stages of the disease; (3) the clinical findings; (4) the results of local reactions to skin tests performed with filarial antigens; and (5) the clinical course subsequent to the onset of symptoms. It is felt that these cases were without doubt individuals who harbored the filarial parasite. However, in but two of our cases were microfilariae demonstrated on blood smear. In other soldiers evacuated from the same areas and with the same symptoms, the adult worm had been demonstrated in biopsies performed elsewhere (Wartman and King<sup>1</sup>). Of particular interest is the fact that the chain of

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symptoms will vary from area to area, and that in many cases the subjective symptoms were rather marked although the physical findings were rather meager. The reverse was also found to be true. Unless one is familiar with the syndrome of "early filariasis," a great many of these cases would in all probability be considered to be functional in origin. The existence of a skin test which has a fairly high degree of specificity is an added objective aid in the diagnosis.

### SYMPTOMS

The earliest symptom in the usual case of filariasis is pain in the scrotal area which is characterized by a feeling of weight and a dull, aching sensation localized to the testicles or to the structures immediately above the testicles. Frequently associated are symptoms of nausea, anorexia, and of deep-seated, generalized aches and pains in the back, arms, and legs. The pain in the legs is commonly found to follow the adductor canal. That in the arms is more generalized and has no characteristic distribution. Back-ache is predominantly lumbar in location.

TABLE I  
Symptoms and History of

| Symptom                             | % of Occurrence |
|-------------------------------------|-----------------|
| Lymphadenitis                       | 63              |
| Swelling in scrotum                 | 61              |
| Pain in testicles                   | 50              |
| Generalized aches and pains         | 42              |
| Nausea and anorexia                 | 35              |
| Pain in arms and legs               | 26              |
| Lethargy, malaise, and fatigability | 22              |
| Lymphangitis                        | 19              |
| Symptoms with work                  | 15              |

Coincident with these symptoms, the individual will frequently observe the development of a rather generalized lymphadenopathy and palpable swelling of the scrotal contents. Lethargy, fatigability, and an increase of all the symptoms on exertion are frequently noted. Lymphangitis is a common occurrence, but was present in only 19 per cent of this series. It is of particular interest to note that in certain areas the individual's first awareness of systemic disease is the accidental finding of an enlargement of the scrotal contents. The subjective symptoms are prone to develop suddenly, are mild to moderate in severity, and are subject to remissions and exacerbations. The frequency of occurrence of symptoms is noted in table I.

### PHYSICAL FINDINGS

Our evaluations of the frequency of various findings must be interpreted in the light of the fact that physical findings in early filariasis are not constant. It has frequently been noted during our period of observation that lymph nodes may vary remarkably in size and that an acutely enlarged gland may diminish in size in a few weeks. Likewise, these patients fre-

quently stated that the degree of funicular enlargement had been much greater at some time in the past. The lymph node involvement was primarily axillary, cervical, and epitrochlear. Inguinal lymphadenopathy was usually discounted unless unquestionably enlarged, as the same degree of lymphadenopathy in this area is frequently to be observed in soldiers returning from tropical service. Lymphadenopathy has not infrequently been found in such unusual areas as the antecubital space and in the intercostal spaces low in the midaxillary line, the latter having been proved by biopsy. The finding of enlarged epitrochlear glands is especially significant. The glands are firm, discrete, and characteristically somewhat tender to pressure. Examination of the scrotal contents may reveal a large firm tender testicle or thickening of the epididymis or enlargement of the funiculus. The latter may present the physical findings of a varicocele with soft, dilated, easily movable veins or an inseparable thickening of all structures of the spermatic cord. Funiculitis is one of the most permanent of all physical findings. Whenever involvement of this structure had been noted at some time in the past, ab-

TABLE II  
Clinical Findings on Our Examination

| Findings        | % of Occurrence |
|-----------------|-----------------|
| Lymphadenopathy | 92              |
| Funiculitis     | 77              |
| Orchitis        | 20              |
| Local edema     | 7               |
| Lymphangitis    | 4               |

normality was still obvious on our examination. This, however, was not true with respect to lymph node involvement. Lymphangitis was infrequent in our experience. One individual, however, experienced repeated bouts of lymphangitis. Each episode was confined to the same area in the forearm and was associated with fever and systemic symptoms which would disappear completely within a week. The frequency of occurrence of physical findings is noted in table 2.

#### LABORATORY EXAMINATION

No characteristic abnormalities were noted on routine laboratory examination. Eosinophilia was not noted. Microfilariae were demonstrated once in our hospital in an individual who had lived for years in an endemic zone in childhood. In another patient, microfilariae were demonstrated in an overseas hospital. Dr. John Bozicevich of the National Institute of Health, Bethesda, Maryland, demonstrated to us the use of a skin test and furnished filarial antigens for the skin testing of all these patients. A detailed description of the skin test, its limitations and specificity will appear presently in a paper by Dr. Bozicevich. The materials used for the testing were a 1:8000 dilution of antigen prepared from the horse filarial worm and the dog heart worm. Both a dog and a horse protein control as well as a saline control were used. In the present series, 88 per cent showed positive

skin reactions whereas 12 per cent were negative. Controlled studies in 49 normal non-allergic individuals who had not been in endemic zones indicated the occurrence of approximately 10 per cent false positive reactions. Studies on 50 allergic individuals from the northern United States without tropical service revealed the presence of 14 per cent false positives. These figures compare favorably with those reported by Wartman and King<sup>1</sup> (90 per cent positive in known cases of filariasis and 10.5 per cent positives in controls) and of those of Bozicevich (to be published).

### PROGRESS AND COURSE OF DISEASE

At the time of admission, most of these soldiers were relatively symptom free. Some complained of generalized aches and pains, persistence of fatigue, and discomfort in the testicular and funicular structures. The majority of these patients were transferred to a reconditioning unit where approximately 25 per cent complained of increased pain and discomfort in direct proportion to the severity of physical activity of the training. It was found that hot showers and high environmental temperatures frequently caused a transitory exacerbation of symptoms. In a few individuals definite changes in physical findings were observed. One soldier carried a heavy barracks bag approximately one-third of a mile and complained of sharp pain in the funicular area. Within a matter of four hours the funicular structures had trebled their size, were tense, and exquisitely tender. This subsided to the previous level within five days of bed rest. In several others unquestionable enlargement of lymph nodes occurred following physical activity. In general, however, continued physical training over a period of three to four weeks resulted in progressively fewer complaints. Although periodic recurrences of systemic symptoms were noted, these became less severe.

### CONSIDERATIONS REGARDING THE MECHANISM RESPONSIBLE FOR SYMPTOMS

The exact anatomical and physiological basis for production of symptoms is unknown. Mechanical blockage by the parasite undoubtedly is a prominent factor in the late and irreversible stages of the disease. The rapid appearance and subsidence of lymphangitis, lymphadenitis, and funicular enlargement suggests a less permanent and more readily reversible cause. In this connection, an inflammatory or an allergic response bears consideration. In the early cases the former has not been demonstrated. In this study there have been several factors suggesting that these responses may be allergic in their origin. This was first brought to our attention by the occurrence of a cyclically recurring erythema in an individual, who following intradermal skin test with the horse antigen, presented an erythematous reaction in the skin test site each afternoon for a period of five days. This same occurrence although less intense and lacking in periodicity has

been noted in several other patients. In one individual this occurred over a period of several weeks. Certain types of filariasis are characterized by the periodicity of appearance of microfilariae in the blood stream. These observations suggested that periodically there existed in the circulating blood a material to which the skin test area had been sensitized. This suggested an Arthus type of reaction to a circulating antigen. It is not difficult to assume that a similar reaction might well occur in internal organs or in glands or in funicular structures and be responsible for both symptoms and physical findings. The skin test itself appears to be a measure of local sensitivity to tissues sensitized by the filarial antigen. Allergic responses in general are characteristically sudden in onset, frequently rapid in subsidence with complete or almost complete reversibility of local tissue changes. After repeated allergic insults a particular tissue may show residual inflammatory infiltration and fibrosis. The evanescent nature of the initial symptoms, the occasional rapid appearance and disappearance of physical findings, the occurrence of symptoms under activity when microfilariae might mechanically be discharged from the parent worm and the reported occurrence of eosinophilia during acute exacerbations suggest that these may well be on an allergic basis. Were mechanical blockage of lymph channels responsible for these symptoms, such transient and reversible reactions would not be expected. It has been quite well established by Wartman, King and others that an acute pyogenic process is not present in these early cases and it would, therefore, appear that an allergic response to the filarial antigen may be responsible for many of the symptoms and physical findings of early filariasis.

### DISCUSSION

There is no one constant chain of symptoms by which the diagnosis of filariasis can be made. There is considerable variability in these initial symptoms depending upon the area in which infection takes place. In certain areas the disease is ushered in by a variety of complaints including lethargy, fatigability, generalized aches and pains, anorexia, and digestive disturbances, whereas in other areas a few hundred miles away, these symptoms are conspicuous by their absence, and the first indication of disease is the accidental finding of a funicular enlargement. In general, however, the following may be considered as the average clinical history and physical findings. After a period of approximately one year in an endemic zone the individual is likely to experience mild, generalized aches and pains, testicular pains, malaise, and systemic symptoms of an infection, and at about the same time, a more or less generalized lymphadenopathy and a funiculitis will be observed. The occurrence of lymphangitis is of great diagnostic importance, but is frequently absent. The incubation period in our series varied from two to 22 months and is undoubtedly related to the density of filarial infestation in the area and to the degree of nocturnal exposure to mosquito bites. This was found to vary considerably on different islands, but was relatively constant

on any one particular island. The fact that microfilariae are infrequently found in the blood stream of these soldiers is not surprising, as Byrd and St Amant<sup>2</sup> in a survey of the native population in American Samoa state that microfilariae are rarely found in the blood stream under five years of age, and that advanced physical findings of filariasis rarely develop before the twentieth year of life. We have examined a group of individuals who have spent considerable time in filarial areas and who were evacuated to the United States for reasons other than filariasis. These examinations and skin tests have been entirely negative suggesting that they either escaped the infection entirely or were so minimally infected that neither clinical symptoms and physical findings, nor cutaneous hypersensitivity could develop. The fact that once removed from an endemic area these soldiers do not experience frequent recurrence of symptoms and further that they showed regression and not progression of physical findings indicated that reinfection and probably also density of infection influences the time of occurrence, the severity and extent of symptoms and physical findings, and the clinical course of the disease. The life span of the adult worm and the length of survival of microfilariae are unknown. These undoubtedly have a rather definite limit of survival and it is reasonable to expect that in the course of time and in the absence of reinfection the symptoms of filariasis should diminish. From our observation of these patients during their period of hospitalization and from a number of follow-up letters, this concept would appear to be substantiated.

The primary reason for the early diagnosis of filariasis and the importance of recognizing the early manifestations lies in the province of preventive medicine. It is felt that early evacuation from an endemic zone will permit the disease to subside or possibly to disappear completely before irreversible changes occur. It is likewise important to recognize the early symptoms of the disease and their variability as many of these individuals would otherwise be considered as having functional disorders and might thus be denied the benefits of early evacuation to a non-filarial area. There is at present no certainty that avoidance of reinfection will prevent progression of the disease or the occurrence of complications at some later date. However, at present the evidence clearly indicates that in the early stages at least, avoidance of reinfection or removal to a temperate climate or both has resulted in a diminution in the frequency and severity of the symptoms and has been attended by a recession of physical findings.

### SUMMARY AND CONCLUSIONS

From an analysis of 100 cases of early filariasis the following conclusions appear justified.

- 1 The diagnosis of filariasis can be made in early cases prior to the appearance of microfilariae in the blood stream and prior to the formerly accepted physical findings.

2. The subjective symptoms are variable and may vary from area to area but the physical findings are quite constant for groups from all areas

3. Certain evidence suggests that the symptoms and perhaps the physical findings of early filariasis are due to an allergic response of tissues sensitized to a circulating filarial antigen

4. Experience thus far suggests that avoidance of reinfection will permit regression of symptoms and signs, and the probable eventual attainment of a completely asymptomatic state

#### BIBLIOGRAPHY

1. WARTMAN, WILLIAM B, and KING, BOYD G Early filariasis in American soldiers—  
Special article in Bull U S Army Med Dept, 1944, lxxvi, 45
2. BYRD, ELON E, and ST AMANT, LYLE Filariasis among Marines Tutuila, Preliminary  
Epidemiological Investigation (Unpublished)

# STUDIES OF FILARIASIS IN SOLDIERS EVACUATED FROM THE SOUTH PACIFIC\*

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IN recent months soldiers,<sup>1</sup> sailors and marines<sup>2, 3, 4, 5, 6</sup> have been evacuated to continental United States from various islands in the South Pacific Area because of suspected filariasis. The present report deals with our findings in 145 soldiers so evacuated, studied at Harmon General Hospital

## OUTLINE OF STUDY

The patients studied had spent from two to 23 months (average 14 months) on tiny islands in the South Pacific on which filariasis due to *Wuchereria bancrofti* is endemic<sup>7, 8</sup>. The islands included Tongareva (Penryhn Island), Bora Bora, Aitutaki of the Cook Islands, Wallis Islands, Samoan group, Tongatabu, Woodlark Island, and the Ellice Islands.

The men had been evacuated from the endemic area within a few weeks of the time that the first symptoms appeared which were considered to be suggestive of filariasis. They arrived at Harmon General Hospital on the average in about two and one-half months after the onset of first symptoms. These facts must be kept in mind in any consideration of the probable future course and prognosis in these men. In contrast with the situation usually existing among natives exposed to repeated infections over years of time,<sup>9, 10</sup> these soldiers spent a comparatively short time in the endemic area under relatively good living conditions and were evacuated as quickly as practicable after the appearance of symptoms thought suggestive of filariasis.

The patients reached Harmon General Hospital in convoys over a period of about four and one-half months. Here they were studied and followed over an average period of about two and one-half months. In addition to the routine history, physical examination, and laboratory tests, special studies included detailed history as to place and duration of oversea duty with reference to the earliest symptoms and the course of the disease, repeated examinations as regards lymphadenopathy, lymphangitis, and spermatic cord and scrotal abnormalities, made in cooperation with genito-urinary consultants, examinations of the stools for ova and parasites, repeated examination of the blood for microfilariae both by day and at night, with ordinary blood smears taken on at least seven days and examinations using the Knott concentration technic on at least three days, in certain patients microscopic

\* Presented in abstract form by Colonel Alexander Marble at the War Session of the American College of Physicians in Chicago, April 1 1944



examination of excised lymph nodes with a search for adult filariae, and in a few patients roentgenograms of the scrotum to detect calcified remains of parasites. Studies regarding intracutaneous and complement fixation tests will be presented later in the paper.

### CLINICAL FINDINGS

It is impossible to present data of absolute accuracy regarding the onset, course and findings of the soldiers while in the endemic area. Many of the men were not hospitalized so that the medical records were incomplete. The summary of oversea findings as presented below is based on available medical records supplemented by the histories given by the soldiers themselves.

The acute symptoms at onset of the disease were those of lymphadenitis often with mild systemic manifestations such as malaise, nausea, vomiting, and pain in the lower abdomen. Swelling and tenderness of lymph nodes were noted usually in the inguinal region although often, axillary, cervical, and epitrochlear nodes were affected. Often present was unilateral scrotal involvement, especially on the left, with funiculitis, epididymitis, and swelling of the scrotal skin. Accompanying this there was in some cases a frank lymphangitis of retrograde type with development of the process away from the node. These manifestations of the acute stage lasted usually three to five days and in only a few cases were accompanied by significant fever or chills. The impression was gained from the soldiers included in our group that most of them were never very ill. The residual findings following acute episodes such as those described consisted of enlarged lymph nodes, induration along the lymphatic trunks with nodular thickenings, induration and tenderness of the spermatic cord, in some patients varicocele, and in rare instances hydrocele of a transient character.

Not all of the soldiers by any means had acute symptoms such as just described. In many of the men the presence of filariasis was not seriously considered until the time of a special physical examination made during a survey for possible cases. At this time the residual findings such as those just mentioned were noted in many of the soldiers, these heretofore had been regarded by the men themselves as due to various causes other than filariasis. On closer questioning some of them gave a history of having had three or four months before, a mild illness which may well have represented an acute phase of the disease. Once the symptoms and signs of filariasis were evident to medical attendants, soldiers were evacuated to the United States as soon as practicable. Included in the group evacuated to the United States were, no doubt, some who probably had no filarial infection whatsoever but in whom adenopathy and other findings, including a possible varicocele, were present before entrance into the endemic area or were acquired there from causes other than filariasis. The evacuation of such men was justifiable, however, so as not to expose to further infection any man who might have acquired the disease, even though in a mild form.

Upon arrival at Harmon General Hospital the men were, in general, in fairly good physical condition and had it not been for the necessity of observing them over a considerable period of time and the uncertainty with which their future was viewed, particularly at first, many of them could have gone to duty almost immediately. Physical examination revealed in almost

TABLE I  
Symptoms and Signs of 145 Patients with Suspected Filariasis

|                              | Lymphadenopathy |          | Lymphangitis |          | Scrotal edema |          | Funiculitis |          | Orchitis |          |
|------------------------------|-----------------|----------|--------------|----------|---------------|----------|-------------|----------|----------|----------|
|                              | No              | Per Cent | No           | Per Cent | No            | Per Cent | No          | Per Cent | No       | Per Cent |
| During first attack overseas | 135             | 93       | 19           | 13       | 18            | 12       | 119         | 83       | 38       | 26       |
| At Harmon General Hospital   | 123             | 85       | 6            | 4        | 10            | 7        | 127         | 88       | 8        | 6        |

all of them enlargement of the inguinal, cervical, axillary and epitrochlear nodes. In many cases, however, it was difficult to decide just how much more than normal such lymphadenopathy was. Most of the lymph node enlargement was inguinal, more commonly on the left than the right side. Most frequent findings included thickening and tenderness of the spermatic cord especially on the left, varicocele especially on the left, and subcutaneous nodules or thickenings along previously involved lymphatic trunks. Following return to the United States and during a period of observation for two to six months at Harmon General Hospital, only six of the men had bouts of lymphangitis, which were uniformly mild. Of the six patients, two have had two attacks since return to this country. It is of interest that despite the predominant inguinal adenopathy, in every case but one the attacks of lymphangitis affected an upper, rather than a lower extremity. A given attack lasted from two to 10 days and as stated before, was accompanied by little or no fever, only one man developing a temperature as high as 101° F. Following a bout of lymphangitis the lymphatic trunk involved was frequently indurated with thickened, nodular formations throughout the affected course. In no case did elephantiasis occur either overseas or at Harmon General Hospital and in only a few instances was there even transient swelling of an extremity.

During the period of observation at Harmon General Hospital the tendency was definitely toward restoration to normal. The size of the lymph nodes tended to decrease, the tenderness and thickening of the spermatic cord tended to disappear and at the time of discharge from the hospital the condition of the men was almost invariably such as to allow them to pass a routine physical examination.

As part of the study the men were housed for at least two to four weeks

in convalescent barracks where graduated exercise was given leading up to five mile marches as a physical test prior to return to duty. In only three instances in whom attacks of lymphangitis were apparently precipitated, did exercise aggravate the condition. Furthermore, the attacks experienced by these three men were said by them to be not so severe as earlier episodes.

Examination of the blood for microfilariae was carried out with each patient on at least seven nights by the usual technic and three days by the Knott concentration method. This study revealed microfilariae in two instances and in these men the finding was made in each only once. In two other patients, microfilariae had been found in the blood overseas on one occasion each, in one man at a Station Hospital and in the second at Tripler General Hospital. Thus of 145 men, in only four were microfilariae found at any time and then on only one occasion in each patient. It should be pointed out that the disease observed in our patients was apparently of non-periodic type since this is the type of filariasis endemic in the area in which these soldiers served.

Routine laboratory studies in general yielded normal findings. The examination of the urine in almost all instances was normal. In keeping with the usual experience with the non-periodic type of filariasis, no case of chyluria was seen. No case of significant anemia was found, the white blood cell count in most patients was entirely normal and in no case significantly elevated, and the blood sedimentation rate was normal. In 47 patients the percentage of eosinophiles in the blood was 4 or greater at one time or another during the period of observation. The findings as regards eosinophilia in the 47 cases were in detail as follows: 4 per cent, 14 cases, 5 to 9 per cent, 21 cases, 10 to 14 per cent, three cases, 15 to 19 per cent, three cases, and 20 per cent and over, two cases.

In only four of these 47 were there significant findings in the routine stool examinations. Cysts of *Endamoeba coli* were found in two of these, each of whom had 7 per cent eosinophiles in the blood. Of the other two patients, one had *Trichuris trichiura* in the stools, with 10 per cent eosinophiles in the blood on one occasion and 17 per cent at another. In the stools of the second, ova of *Necator americanus* were found, this patient had 6 per cent eosinophiles in the blood. In the remaining 41 patients no cause for eosinophilia was found other than filariasis. This was true even in one patient in whom eosinophilia amounted to 18, 29, and 69 per cent in January, February and March (1944) respectively, and in a second in whom 35 per cent was found in December 1943 and 58 per cent in March 1944.

In 19 patients lymph nodes were excised and studied microscopically. Careful examination failed to reveal filariae or remains of filariae in the sinuses or perivascular lymphatic channels. This experience is somewhat at variance with that of certain other observers<sup>1,4</sup> and may reflect a milder degree of infection in our cases. The lymph nodes in our patients were not normal, however, showing changes considered characteristic of a reactive lymph node. There was, in general, a lack of preservation of lymph follicle



In the intracutaneous tests, both direct and passive transfer technics were carried out in the usual manner. For direct tests, the outer aspect of the upper arm was used and intracutaneous blebs were made with the antigens and control materials (horse protein and dog protein in dilutions corresponding to the filaria antigens; 0.3 per cent phenol in physiologic solution of sodium chloride) in the different dilutions. A bleb about 6 mm in diameter was formed by the injection of 0.05 c.c. of the test material. If in 20 minutes a wheal, associated with pseudopods and a zone of erythema, developed with a diameter which exceeded by at least 3 mm that of the initial bleb (with allowance for the reaction produced by the control substance), the response was considered to be a positive immediate reaction. The test sites were reexamined for delayed reactions after 24 hours.

Passive transfer tests were made by the standard method of Prausnitz and Küstner, allowing a 48 hour interval before testing the sensitized sites in the recipients with dilutions similar to those used in the direct intracutaneous tests.

In both the direct and passive transfer tests, the reacting wheals were outlined with ink and transcribed on tracing paper on which measurements were made. The records were filed for future reference.

The complement fixation tests were carried out at the National Institute of Health, using a saline antigen prepared from *D. immitis* using the technic described elsewhere.<sup>16</sup>

**Results—Direct Intracutaneous Tests.** In table 2 are shown the results obtained in the direct intradermal tests. The 106 control subjects were physically fit soldiers who had never been outside continental United States.

TABLE II  
Results of Direct Intracutaneous Tests

| Subjects Tested                  | Total Cases | <i>D. immitis</i> —1:8000 |                 |                   | <i>S. equine</i> —1:8000 |                 |                   | Total Positive |          |
|----------------------------------|-------------|---------------------------|-----------------|-------------------|--------------------------|-----------------|-------------------|----------------|----------|
|                                  |             | Number Tested             | Number Positive | Per Cent Positive | Number Tested            | Number Positive | Per Cent Positive | No.            | Per Cent |
| Controls                         | 106         | 106                       | 4               | 4                 | 106                      | 5               | 5                 | 6              | 6        |
| Patients with suspected filariae | 140         | 110                       | 65              | 46                | 130                      | 67              | 48                | 76             | 51       |

Among these there were four who gave a positive response to a 1:8000 dilution of *D. immitis* and five to a similar dilution of *S. equine*, or six in all who gave positive reactions to either or both of the antigens. Two others of the 106 subjects gave positive reactions to a 1:4000 dilution of *D. immitis*. The slides of the eight subjects mentioned were not available for examination for parasites or ova. Although on subsequent questioning all of the eight gave histories suggesting altered skin sensitivity as indicated by prevailing or recent attacks of dermatitis venenata, trichophyton infection, seborrheic

dermatitis or urticaria, no great importance can be attached to this information since it was not possible to question closely the remaining 98 control subjects

Among the 145 patients with suspected filariasis, there were 140 who were tested with 1 8000 dilutions of *D immitis* and *S equina*. An additional seven patients (including two not in the total of 140 listed in table 1) gave positive reactions to a 1 4000 dilution of *D immitis*, counting these, there were 83 or 58 per cent of 142 patients who gave positive tests

*Passive Transfer Tests* Passive transfer studies were carried out with the sera of 140 patients with suspected filariasis, using non-sensitive recipients as the test subjects. Positive results were obtained in 24, or 17 per cent, using *D immitis* antigen, and in 35, or 25 per cent, using *S equina* antigen, both in 1 8000 dilution. All told, there were 41 cases, or 29 per cent, in whom positive tests were obtained with either or both antigens in 1 8000 dilution. In two other cases, positive results followed the use of *D immitis* antigen in 1 4000 dilution.

*Complement Fixation Studies* Complement fixation tests carried out at the National Institute of Health gave positive results with the sera of 95, or 66 per cent, of 143 patients so studied. Since the experience with complement fixation tests in filariasis is relatively meager it was considered desirable to establish the degree of specificity of the test by a study of apparently normal individuals. In one series of 39 soldiers who had never been outside continental United States and whose home was in the northern half of the United States, positive complement fixation tests for filariasis were obtained in 10, or 25 per cent. These subjects were hospital patients who were convalescing from surgical, chiefly orthopedic, disorders of a nature as to make them "normal" for the purposes of the present study. In all cases examinations of the stools were carried out for ova and parasites and in only one patient were the tests positive, in this man on each of two examinations ova of *Necator americanus* were found.

As a second series of control subjects, 81 normal soldiers from Camp Fannin, Texas, were studied. Blood was drawn on the day of, and just following, the completion of a physical examination qualifying them for overseas service. All of the men were from the northern half of the United States and none had been in the Army more than four months. The following were the results of the complement fixation tests

|                   |       |
|-------------------|-------|
| Negative          | 56    |
| Positive          | 13    |
| Doubtful          | 11    |
| Anticomplementary | 1     |
|                   | <hr/> |
|                   | 81    |

Of the 81 tests 13, or 16 per cent, were definitely positive. The high percentage of doubtful reactions was probably due to deterioration of certain of the sera incident to time required for transportation and storage. If one

excludes these from the series, thereby reducing the number to 70, then the 13 positive tests represent 19 per cent of the total. It is our belief that if the 11 samples had been suitable for testing, most of them would have been negative since over-long storage has a tendency to increase the binding power. Although the control data are unsatisfactory, the results indicate that the complement fixation test as carried out was positive in from 16 to 25 per cent of persons with no history of filariasis.

Thinking that perhaps the positive tests in these control groups were due to present or past trichina infestation, the sera of four of the men giving positive tests in the first group of 39 and eight of those giving positive tests in the second group of 81, were tested with trichina antigen. All were negative.

The anomalous results obtained in the case of these control individuals led to an investigation of the possible cause\*. In later antigen preparations, it was found that certain lots contained an unusual degree of opalescence apparently due to marked colloidal particulation. Titration of these antigens with the complement in overnight instead of the usual one hour fixation indicated marked anticomplementary properties. Since overnight titration for binding power was not conducted routinely with the tests reported above, it is probable that the positive results in some cases at least were due to a similar anticomplementary property of the antigens employed. No doubt further study will disclose additional factors responsible for the lack of specificity of the test in certain cases.

TABLE III  
Comparison of Results of Direct Intracutaneous and Complement Fixation  
Tests Using *D. immitis* Antigen

| Intracutaneous | Complement fixation |    |   |    |   |
|----------------|---------------------|----|---|----|---|
|                | +                   | +  | 0 | 0  | + |
| +              | 58                  |    |   |    |   |
| 0              |                     | 33 |   |    |   |
| +              |                     |    | 7 |    |   |
| 0              |                     |    |   | 12 |   |
| No test        |                     |    |   |    | 4 |

direct intracutaneous tests and 95 positive complement fixation tests. Of the total of 140 patients (excluding thereby the four patients who had complement fixation but no intracutaneous tests), in 100 or 71 per cent, there was agreement between the two tests, intracutaneous and complement fixation. In 33 instances, or 24 per cent, the complement fixation test was positive whereas the intracutaneous test was negative. In seven instances, or 5 per cent, the reverse was true.

In table 4 a similar comparison is made between the results of the complement fixation test and the direct intracutaneous test using a 1:8000 dilution of *S. equina*.

TABLE IV  
Comparison of Results of Direct Intracutaneous and Complement Fixation Tests Using *S. equina* Antigen

| Intracutaneous | Complement fixation |    |    |    |   |
|----------------|---------------------|----|----|----|---|
|                | +                   | +  | 0  | 0  | + |
| +              | 55                  |    |    |    |   |
| 0              |                     | 35 |    |    |   |
| +              |                     |    | 12 |    |   |
| 0              |                     |    |    | 37 |   |
| No test        |                     |    |    |    | 5 |

It is evident that there were 67 positive direct intracutaneous tests using *S. equina* in 1:8000 dilution. As stated before, there were 95 positive complement fixation tests. Of the total of 139 patients (excluding thereby five patients who had complement fixation but no intracutaneous tests), in 92 or 66 per cent, there was agreement between the two tests. In 35 instances, or 25 per cent, the complement fixation test was positive whereas the direct intracutaneous test was negative. In 12 instances, or 9 per cent, the reverse was true.

From the above it is evident that in 66 to 71 per cent of the cases there was agreement between the results of the complement fixation and the direct intracutaneous tests. This percentage, although not as high as might be desired, is nevertheless, great enough to indicate the possible value of the combined use of these two types of tests in the diagnosis of filariasis, particularly if the complement fixation test can be made more specific.

*Intracutaneous Tests with Other Filarial Antigens.* In addition to the intracutaneous tests carried out with high dilutions of *D. immitis* and *S. equina* antigen, direct and passive transfer tests were done in 75 of the patients with suspected filariasis using a 1:200 dilution of an antigen prepared from *Litomosoides carini*, a filaria obtained from the cotton rat. This antigen was kindly supplied by Dr. H. M. Rose of the College of Physicians and Surgeons of Columbia University. Of the 75 patients tested, 58 or 77



per cent, gave positive reactions in direct tests. Of 50 patients tested, 23 or 46 per cent, gave positive reactions in passive transfer tests. Comparison of the results obtained in the direct intracutaneous tests and in the complement fixation tests shows agreement in 49 or 66 per cent of 74 patients with whom both tests were carried out. The use of a 1:200 dilution of *L. carinii* was not carried further because it is believed that in this relatively high concentration falsely positive tests are likely to be obtained. These falsely positive skin reactions due to sensitiveness to helminth and other related antigens may be avoided by the use of a filaria antigen in high dilutions such as 1:8000.

*Intracutaneous Tests with Antigens Other than Those of Filarial Origin*  
Of 87 cases tested intracutaneously with both *D. immitis* and *Trichinella spiralis* antigens, each in 1:8000 dilution, 48, or 55 per cent, gave positive immediate reactions to the former antigen but in only three cases, or 3.5 per cent, to the latter. In these three cases, positive reactions were obtained also with the *D. immitis* antigen. In these combined immediate reactions, the predominant reactions as measured by the diameter of the wheals were obtained with the filaria antigen. In 30 patients in whom passive transfer tests were done, positive wheal reactions were obtained in 21 per cent with *D. immitis* antigen in 1:8000 dilution with no positive wheal reactions when trichina antigen in like dilution was employed.

Forty-seven patients were tested with *L. carinii* antigen in 1:200 dilution and *Ascaris lumbricoides* extract in 1:100 dilution. The following results were obtained. In direct intracutaneous tests, 41, or 89 per cent, gave immediate positive wheal reactions with *L. carinii* antigen, whereas 20, or 42 per cent, gave immediate positive wheal reactions with ascaris extract. In passive transfer tests in 30 cases, eight, or 27 per cent, gave positive wheal reactions with *L. carinii* antigen whereas 5 or 17 per cent, gave positive immediate reactions with ascaris extract.

Because the clinical picture in filariasis was characterized by inguinal adenopathy and involvement of the scrotal structures in the majority of the filaria cases observed here, a differentiation from lymphogranuloma inguinale was desirable. In this connection the intracutaneous reaction is helpful. In 84 cases intradermal tests with Frei antigen (Lygranum) against a suitable control were made and read after a 24 and 72 hour interval. In these cases only two positive reactions were observed. In this same group of cases approximately 50 per cent gave positive reactions with *D. immitis* antigen in 1:8000 dilution and 89 per cent gave positive reactions with *L. carinii* in 1:200 dilution.

## DISCUSSION

The clinical findings presented in the first part of the paper are almost identical with those reported by others<sup>1,2</sup> who have observed American troops similarly affected. It is obvious that in our patients the infection was of mild degree. This may explain why in none of 19 cases studied were adult worms or remains of worms found on microscopic examination of excised lymph nodes. It is of interest that, despite this, microfilariae were demonstrated in the blood on one occasion in each of four patients (the positive smears were found at oversea hospitals in two of the patients).

Unfortunately, in persons so mildly infected as these men, it is difficult, using ordinary clinical and routine laboratory methods, to be sure of the diagnosis. It appears likely that most of our 145 patients with suspected filariasis actually were so affected. In only 13 cases or 9 per cent of the total, was clinical and laboratory evidence so scant that the diagnosis of filariasis seemed unwarranted. In an additional 10 or 15 per cent of patients the physical and routine laboratory findings were such that, although the diagnosis of filariasis was made, considerable doubt existed that the clinical features—lymphadenopathy, slight scrotal abnormalities and history suggesting a mild, acute phase of the disease some months before—really represented manifestations of filariasis.

Because of these considerations, particular interest was directed toward the results obtained with intracutaneous and complement fixation tests as aids in diagnosis. Although Tahaferro and Hoffman<sup>13</sup> in 1930 and Fairley<sup>11,12</sup> in 1931 and 1932 had carried out such tests, no great amount of work had been done along this line until recently when various workers<sup>1,2,4,5</sup> carried out studies on patients similar to ours. Most investigators have used extracts prepared from *Dirofilaria immitis* although Culbertson, Rose and Demarest<sup>14</sup> used an antigen derived from *Litomosoides carini*.

Most workers have reported approximately 80 to 90 per cent positive direct intracutaneous tests in individuals with suspected filariasis using the antigens named above. However, the findings are open to criticism on two grounds. (a) Most investigators have paid insufficient attention to the strength of the antigen used for skin testing. Studies at the National Institute of Health have shown that when extracts as strong as 1:100 or 1:200 and indeed up to 1:4000 were used, falsely positive results are obtained due to group reactions in patients infected or formerly infected with other helminths. Many of these falsely positive reactions are avoided if dilutions of *D. immitis* antigen of 1:8000 are used. (b) With the status of the test as yet unsettled, an adequate series of normal controls should be tested by those studying cases of suspected filariasis. It is realized that this is impossible in oversea endemic areas, but studies carried out in non-endemic regions should include control subjects with no history of residence in an endemic area. Furthermore, both groups—filaria suspects and normal controls—should have examinations carried out for intestinal parasites. In

our own control series of 106 individuals, six gave positive skin reactions to either or both of two antigens, *D immitis* and *S equina* in 1:8000 dilution, and two others gave a positive response to a 1:4000 dilution of *D immitis*. Wartman<sup>1</sup> states that 10.5 per cent of a control group gave positive reactions. (c) Adequate control tests should be carried out with antigens prepared from dog serum (horse serum if *S equina* antigen is used) and other helminth (ascaris, trichina) antigens if available, in addition to the usual saline control substances.

Not many data are available in the literature regarding the outcome of complement fixation tests in filariasis. Lloyd and Chandra<sup>16</sup> found 23 positive tests in 89 patients with filariasis (26 per cent). Fairley<sup>11, 12</sup> reported positive complement fixation results in individuals with filariasis as did Mohr and Lippelt.<sup>17</sup> The former used an antigen prepared from *D immitis* and the latter investigators one prepared from *Contortospiculum rheae*. Bozicevich and Hutter<sup>18</sup> in the laboratory of the National Institute of Health obtained negative reactions in each of 25 patients from the United States Naval Hospital at Bethesda who had clinical evidence of filariasis with a history of exposure. Changes made later in the technique of the test<sup>19</sup> resulted in marked improvement in the sensitivity. Although in our series of patients with suspected filariasis positive reactions were obtained in 95, or 66 per cent, positive reactions were also obtained in a high percentage, 16 to 25 per cent, of control groups. It is obvious that much more work must be done with the complement fixation test particularly as to its specificity. Further studies both in individuals with undoubted filariasis and in carefully selected control figures are indicated. Unfortunately these studies are made difficult because in the preparation of the antigen, worms for extraction must be obtained from sacrificed dogs or horses, consequently the supply of antigen is apt to be limited and variable.

### SUMMARY

1. Clinical findings and results of intracutaneous and complement fixation tests in 145 soldiers evacuated from the South Pacific Area because of suspected bancroftian filariasis, are presented.

2. Signs and symptoms suggestive of filariasis including lymphadenopathy, lymphangitis, serosal edema, funiculitis, orchitis and varicocele, arose on the average after about 13 months' residence in an endemic area.

3. The symptoms were, in general, mild and only six patients experienced bouts of acute lymphangitis during the period of study in the United States. No case of elephantiasis occurred. No case of chyluria was encountered.

4. Microfilariae were demonstrated in the blood on one occasion in each of four patients (in two of these at overseas hospitals).

6 Microscopic examination of excised lymph nodes in 19 cases showed only a non-specific inflammatory response ("reactive lymph node") No adult worms or remains of worms were seen

7 In four of 29 cases roentgenograms of the scrotum showed tiny areas of calcification However, it is not possible to state that such calcification was due to the presence of *W bancrofti*

8 Direct intracutaneous tests using antigens of *Dirofilaria immitis* and *Setaria equina* in 1:8000 dilution gave positive responses in 54 per cent of cases as compared with 6 per cent in a series of 106 control subjects Of 75 patients tested with a 1:200 dilution of *Litomosoides carini*, 77 per cent gave positive reactions

9 In passive transfer tests positive responses were obtained to either or both *D immitis* or *S equina* antigen in 1:8000 dilution in 29 per cent of cases Of 50 patients tested with a 1:200 dilution of *L carini*, 46 per cent gave positive reactions

10 Positive complement fixation tests were found in 95, or 66 per cent, of 143 patients studied However, the complement fixation technic used can not be considered wholly specific since 16 to 25 per cent of normal control subjects gave positive tests It is believed that improvements being effected in the technic of the test will reduce the number of non-specific reactions There was agreement between the results of the complement fixation tests and the direct intracutaneous tests with *S equina* and *D immitis* in 66 and 71 per cent of patients, respectively

11 No specific treatment was given Therapy included a liberal diet "reconditioning" by means of gradually increasing activity and psychotherapy to allay fears as to possible future complications of the disease The outlook for the men is considered good because of the relatively short residence in the endemic area and the slight degree of infection

#### BIBLIOGRAPHY

- 1 WARTMAN, WILLIAM B, and KING, BOYD G Early filariasis in American soldiers. Bull U S Army Med Dept, No 76, May 1944, 45-49
- 2 DICKSON, JAMES G, HUNTINGTON, ROBERT W, JR, and EICHOLD, S Filariasis in defense force, Samoan Group, U S Nav Med Bull, 1943, xli, 1240-1251
- 3 ROME, HOWARD P, and FOGEL, R HARWOOD The psychosomatic manifestations of filariasis, Jr Am Med Assoc, 1943, cxxiii, 944-946
- 4 MICHAEL, PAUL Filariasis among Navy and Marine personnel Report of laboratory investigations, U S Nav Med Bull, 1944, xlii, 1059-1074
- 5 FLYNN, PHILIP D Filariasis suspects Review of cases admitted, U S Nav Med Bull, 1944, xlii, 1075-1079
- 6 HUNTINGTON, ROBERT W, JR, FOGEL, R HARWOOD, EICHOLD, SAMUEL, and DICKSON, JAMES G Filariasis among American troops in a South Pacific island group Yale Jr Biol and Med, 1944, xli, 529-537
- 7 O'CONNOR, FRANCIS W Researches in the Western Pacific A report on the results of the expedition sent from the London School of Tropical Medicine to the Ellice, Tokelau and Samoan Islands in 1921-1922 1923 J C Philp and Son, London

- 8 BUXTON, PATRICK A. Researches in Polynesia and Melanesia. An account of investigations in Samoa, Tonga, the Ellice Group and the New Hebrides in 1924 and 1925 Parts V-VII. London: The London School of Hygiene and Tropical Medicine, November 1928.
- 9 NAPIER, L. EVERARD. Filariasis due to *Wuchereria bancrofti*. *Medicine*, 1944, **xxiii**, 149-179.
- 10 MANSON-BAHR, PHILLIP H. Manson's tropical diseases, 10th Edition, 1935, Cassell and Company, Ltd., London, pp 686-736.
- 11 FAIRLEY, N. HAMILTON. Serological and intradermal tests in filariasis, *Trans Roy Soc Trop. Med and Hyg*, London, 1931, **xxiv**, 635-648.
- 12 FAIRLEY, N. HAMILTON. The skin test and complement fixation reactions in filariasis, *Trans Roy Soc Trop Med and Hyg*, London, 1932, **xxv**, 220-221.
- 13 TALIAFERRO, WILLIAM H., and HOFFMAN, WILLIAM A. Skin reactions to *Dirofilaria immitis* in persons infected with *Wuchereria bancrofti*, Jr. *Prev. Med*, 1930, **iv**, 261-280.
- 14 CULBERTSON, JAMES T., ROSE, HARRY M., and DEMAREST, CONSTANCE R. *Filariasis bancrofti*: its diagnosis by immunological tests with antigen derived from *Litomosoides carini*, *Am Jr. Hyg*, 1944, **xxix**, 156-162.
- 15 BOZICEVICH, JOHN, and HUTTER, A. M. Intradermal and serological tests with *Dirofilaria immitis* antigen in cases of human filariasis, *Am Jr. Trop Med*, 1944, **xxiv**, 203-208.
- 16 LLOYD, R. G., and CHANDRA, S. N. Complement fixation in filariasis, *Indian Jr Med Res*, 1933, **xx**, 1197-1208.
- 17 MOHR, WILHELM, and LIPPERT, HEINRICH. Bericht ueber weitere Ergebnisse mit der Filarien-Komplementbindungsreaktion, *Klin Wchnschr*, 1940, **xix**, 157-159.
- 18 BOZICEVICH, JOHN, DONOVAN, ANTHONY, MAZZOTTI, LUIS, DIAZ A., FRANCISCO, and PADILLA, ENRIQUE. Intradermal and complement fixation reactions elicited by various antigens in persons infected with *Ochocerca volvulus*. Presented before American Society of Tropical Medicine, St. Louis, Missouri, November 15, 1944.

## THE UNUSUAL IN GASTROINTESTINAL ROENTGENOLOGY \*

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DURING the last 10 years there has been a marked increase in the number of qualified roentgenologists in this country † The fact must be recognized that even with this group of specialists available, a large part of our population depends on internist, surgeon and general practitioner for diagnostic radiographic service It is sincerely believed that the time will come and is not far distant when most cities of 20,000 population will support a qualified radiologist In the meantime, where this service is not available or where the physician prefers to do his own diagnostic radiology, the greatest degree of skill possible must be attained

It is with this thought in mind that a few cases of relatively rare gastrointestinal pathological processes are presented Even the individual who spends all of his time in radiology is prone to ignore the fact that other pathological processes than cancer and ulcer may be visualized It is an axiom that one does not diagnose the pathological process of which he is not aware or of which he does not think

*Esophageal-Pharyngeal Diverticulum* This is a true pulsion type of diverticulum, occurring on the posterior wall at the junction of the pharynx and esophagus Due to anatomical muscular weakness in this area only slight resistance to pressure is offered Once a small mucosal sac develops here, food particles collect and by their weight cause a gradual increase in size until a sac which may become huge forms between the esophagus and spine Pressure forward may be so great as completely to occlude the esophagus Barium solution in this sac is visualized on the fluoroscopic screen as a spherical or ovoid shadow at the level of the junction of the esophagus and pharynx The esophagus, if the pressure is not so great as to occlude it completely, is seen to emerge from it high on its anterior surface

### CASE REPORTS

*Case 1* G M, negro male, aged 55 (figure 1) This greatly emaciated negro man complained of vomiting and weight loss over a period of several months On close questioning he admitted some difficulty in swallowing for five years His main trouble, however, was vomiting after a meal without nausea He attributed his trouble to pleurisy which he developed five weeks previously but which improved

Physical examination revealed emaciation as the prominent finding His voice had a hollow quality No masses were palpated in the abdomen

\* Received for publication March 13, 1945

† In 1930 there were 1,005 radiologists in the United States In 1940, 2,866 physicians stated that they were radiologists—Information from American College of Radiology



FIG 1 Case 1 Esophageal-pharyngeal diverticulum

Roentgenographic examination revealed a large esophageal-pharyngeal diverticulum out of which only a small quantity of barium solution spilled over into the esophagus

Esophagoscopy was attempted but the opening into the esophagus could not be identified



FIG 2 Case 2 Esophageal varices

Gastrostomy was performed but the patient was almost moribund at the time of operation and died a few days later

At autopsy the following findings were recorded "In the upper portion of the esophagus, just at the opening of the esophagus from the pharynx in the posterior wall is a diverticulum which measures  $7\frac{1}{2}$  by  $4\frac{1}{2}$  by 5 inches. This diverticulum lies on the posterior portion of the esophagus over which it hangs. In this way it folds over the opening to the remainder of the esophagus forming a slit-like aperture which under pressure is completely closed."



*Esophageal Varices and Gastric Varices* These varices occur when it is necessary for the esophageal veins to form a collateral circulation. In any case of obscure bleeding from the gastrointestinal tract one should not omit a study of the esophagus and cardia of the stomach for varices. This process is usually not revealed by the routine study. The patient should be supine or in an oblique supine position. He should swallow moderately thick barium solution in a small quantity. Spot films should be made of the entire esophagus. The mucosal pattern will show as irregular trabeculation of negative shadows due to displacement of the barium by the varicose veins. There will be a beaded appearance where the veins are most numerous. Usually only the lower esophagus is involved although the entire esophagus and cardia of the stomach may show the typical pattern of varicose veins.

*Case 2.* H. H., white male, aged 35 (figure 2). The patient's chief complaint was weakness, vomiting of blood, and tarry stools. One week prior to admission into the hospital the patient became nauseated following a big meal and vomited several large blood clots. Vomiting occurred two more times this same day and there was bright red blood the last time. He became weak and faint following this episode. Stools the next day were black. There was no history of illness during the past, but the patient had noticed an enlargement of the abdomen for several years.

Physical examination revealed a mass in the upper left abdomen thought to be the spleen. Blood count was normal except for slight anemia.

Roentgenographic examination was reported as follows: "The esophagus shows a trabeculated pattern characterized by vermiform shadows due to negative filling defects in the barium filled esophagus. The picture is classically that of esophageal varices."

A diagnosis of Banti's disease was made and a large spleen was removed. This weighed 1,070 grams and was reported by the pathologist as showing chronic and acute splenitis.

The patient returned to the hospital four years later because of a profuse gastrointestinal hemorrhage. This was the first severe hemorrhage since the operation. Her hemoglobin was 48 per cent. Roentgenographic examination showed moderate increase in the size of the varices. Treatment consisted of blood transfusions.

*Case 3.* L. S., white female, aged 48 (figure 3). The chief complaint was vomiting of blood and difficulty in swallowing. The patient had had a dull pain in her epigastrium for five years. Five days previously she became nauseated, vomited and passed tarry stools. She became weak and faint following this blood loss. On physical examination the spleen was not palpated and the liver was thought to be moderately enlarged.

*Achalasia of the Esophagus* This condition of achalasia of the esophagus is more commonly known as cardiospasm. Barium is not permitted to enter the stomach readily. The point of obstruction is at the cardia. If it is higher than this it must not be considered achalasia. The lower or cardiac end of the esophagus presents a smooth tapering conical contour as contrasted to the irregular contour of malignancy. Marked dilatation of the



FIG 3 Case 3 Gastric varices

esophagus is the rule with long standing achalasia. Apparent cardiospasm in an old person with but little dilatation must be looked on with considerable suspicion, as an early carcinoma may resemble or produce cardiospasm. Inhalation of the fumes of an amyl nitrite pearl is a valuable means of making a differential diagnosis if in doubt. The spasm is usually relaxed in a few minutes if it is a spasm and not organic obstruction. In some cases the soft tissue shadow of the esophagus before barium is given will form a

*Case 6* D D, white female, aged 18 (figure 6) The patient complained of headaches, nausea and a mass in the abdomen Six months prior to admission the patient was awakened one morning with a sudden sharp abdominal pain This lasted two days and gradually disappeared A small mass was found by the patient at this time This mass has gradually increased in size There was no other significant history-obtained until after the operation Then the patient's mother told of the child



FIG. 5. *Case 5* Hiatal hernia

patient's mother told of her and swallowing the hair, as a habit This habit started at

Roentgenographic examination was reported as follows "As the barium solution enters the stomach it appears to spread in all directions about a mass occupying the central portion of the stomach, causing the stomach contour to be clearly outlined with an area of central translucency. The barium visualizes a wide tube-like second and third portion of the duodenum. A constriction is seen in the barium column as it crosses behind the pylorus and another at the ligament of Treitz.



FIG 6 Case 6 Trichobezoar

At operation a mass of hair forming a cast of the stomach and duodenum was removed. The postoperative recovery was uneventful.

*Benign Tumors of the Small Intestine* Tumors of the small intestine are very rare. Raiford<sup>2</sup> found in a series studied at Johns Hopkins Hospital 6.5 per cent of all tumors in the gastrointestinal tract arising from the

small intestine Tumors of the carcinoid type were found to be infrequent The "argentaffective tumors" or carcinoid tumors have their habitat chiefly in the cecum, terminal ileum, appendix, or sometimes in the ascending colon.<sup>2</sup> In the case described an important characteristic of the small intestinal tumor is demonstrated This is the tendency of such a tumor to produce intussusception into the adjacent cecum A large negative shadow is seen which resembles and may perhaps not be differentiated from a primary tumor of the cecum, as seen roentgenographically

*Case 7* L T, white male, aged 50 (figure 7). The chief complaint was a lump in the lower abdomen and occasional colicky pain The pain was first observed one month prior to admission, following a meal Several similar attacks had occurred There had been 15 pounds weight loss during the preceding two months



FIG 7 *Case 7* Intussusception of benign tumor of terminal ileum into cecum Contrast enema and air instillation

Physical examination revealed a semifluctuant tender mass in the lower right quadrant This was about the size of a small lemon

Roentgen examination visualized a filling defect in the cecum as it was filled with barium solution A mass could be palpated here Barium could not be forced through into the terminal ileum It was thought to be a primary carcinoma of the cecum

At operation the cecum was found enlarged owing to an intussusception The intussusception was chiefly the last six inches of the terminal ileum invaginated into itself and into the cecum After the invagination was freed a small tumor was found in the terminal ileum three inches from the ileocecal valve Opposite the tumor in the mesentery were many enlarged glands The wall of the ileum was thickened

Pathological report was as follows. "Ulcerating argentaffective tumor or carcinoid of the terminal ileum with metastasis to the regional lymph nodes"

*Regional Ileitis* Granulomata of the ileum were described in medical literature by Combe and Saunders in 1806<sup>3</sup> During recent years many papers on the subject have appeared The condition has been described under various names Dalziel called it "hyperplastic enteritis"<sup>4</sup>; Crohn, Ginzburg and Oppenheimer referred to that type involving the terminal ileum



FIG 8 Case 8 Regional ileitis Double contrast enema

as "regional ileitis"<sup>5</sup> Harris, Bell and Brunn described the process under the term "cicatrizing enteritis,"<sup>6</sup> and Carr and Boeck suggested the name "chronic ulcerative enteritis"<sup>7</sup>

Pathologically segments of the ileum, jejunum and even the colon may be involved The segment of the gut involved in the process is thickened and edematous The mucosa is ulcerated and in some cases hyperplastic

Mesenteric glands are enlarged Tubercle like structures may develop on the serosa Later, cicatrization occurs

The lesion may be detected with serial films of the small intestine after a barium meal If the terminal ileum is involved it is best studied by a reflux of barium solution through the ileocecal valve into the terminal ileum Early



FIG 9 Case 9 Carcinoma of sigmoid Double contrast enema

in the disease the gut involved will show only slight narrowing of the channel, rigidity and possibly ulceration Later the marked narrowing results in the "string sign "

Case 8 White female, aged 20 (figure 8) The patient complained of pain in the right side This had been present for two years One year prior to admission she developed painful subcutaneous nodules which were diagnosed erythema nodosum These disappeared after one month Recently she had developed weakness, nausea and pain in the side The pain was cramp-like "as though something were trying to pass an obstruction "

Physical examination revealed a tubular non-tender mass just to the right of the umbilicus

Roentgenographic examination revealed "a hyperplastic type of infiltration of the terminal ileum and cecum. The ileum throughout the terminal nine inches could be palpated as a tender, rope-like structure. The cecal head is also deformed." A diagnosis of regional ileitis was made



FIG 10 Case 10 Ureteral-rectal fistula

**Operation** This consisted of removal of 35 cm of terminal ileum, the cecum and 15 cm of ascending colon

**Pathology** "Chronic ulcerative granulomatous enteritis and cecitis, chronic granulomatous peritonitis, localized, chronic hyperplastic lymphadenitis"

The patient returned to the hospital two weeks after the first dismissal with a rectal fistula at the site of the previous operation. She had a diarrhea which soon became bloody. Roentgenographic examination showed a narrowed segment in the transverse colon and ulceration of the descending colon. Her condition became steadily worse. She died three months after the operation. There was no autopsy.



*Contrast and Double Contrast Enemas* Examination of the colon is most satisfactorily accomplished with the contrast enema. Study of the colon with the barium meal is inconclusive and may be a dangerous procedure if there is obstruction. For visualization of the mucosal pattern, polyps and occasionally tumors the double contrast enema is valuable.

We wish to stress briefly the value of the double contrast enema in visualization of carcinoma of the colon. The colon is first carefully studied with the contrast enema. Following evacuation, with as little delay as possible, under fluoroscopic control enough air is instilled into the colon to fill it completely. Films are of more value than the fluoroscopic examination in making the final diagnosis. Often if the colon is redundant, the point of obstruction is visualized poorly because of superimposed overlying coils of gut. With the contrast enema this handicap is often overcome and the tumor will be seen invaginating into the air filled colon (figure 9).

*Case 9* White female, aged 60 (figure 9). This patient had an occasional cramp-like pain but the predominating symptom was constipation. There was no blood in the stool. With the barium enema a point of obstruction was demonstrated with considerable difficulty because of a markedly redundant colon. No barium solution could be forced past the point of obstruction. A subsequent air injection not only demonstrated accurately the point of obstruction at the junction of the sigmoid and descending colon but showed it to be a medullary type of tumor.

At operation a medullary carcinoma of the colon was removed.

*Case 10* M S, colored female, aged 36 (figure 10). The patient's chief complaint was watery, frequent bowel movements. Five years before this the patient had had a hysterectomy for uterine fibroids. The postoperative course was uneventful except for a period of chills and fever lasting four days. The watery stools had been present for about three years when she was seen in the out-patient clinic.

Roentgenographic examination. "A normal colon is visualized. The kidney and ureter on the left are visualized as normal structures by the barium solution. The ureter can be seen to blend into the rectal shadow." A diagnosis of uretero-rectal fistula was made. This was subsequently verified by urological examination.

Surgical repair was refused by the patient.

## CONCLUSION

The roentgenologist must have a sound background of pathology. It is not sufficient that he describe a pathological process. He must be able to express an idea as to the nature of the pathological process, the shadow of which is seen on his fluoroscopic screen or film. He will not be correct in every case but his opinion will gain respect as he develops skill and experience and above all as he develops a knowledge of the gross pathological possibilities.

## BIBLIOGRAPHY

- 1 RAIFORD, T S Tumors of the small intestine their diagnosis with special reference to the x-ray appearance, *Radiology*, 1931, xvi, 253-279
- 2 HERTZLER, A E Surgical pathology of diseases of the gastrointestinal tract, 1936, J B Lippincott, Philadelphia, p 207

- 3 ABEL, I Acute abdominal catastrophes, Jr Am Med Assoc, 1937, cix, 1241-1245  
(GOLDSTEIN in discussing paper by ABEL)
- 4 DALZIEL, T K Chronic interstitial enteritis, Brit. Med Jr, 1913, ii, 1068-1070
- 5 CROHN, B B, GINZBURG, L, and OPPENHEIMER, G D Regional ileitis, a pathological and clinical entity, Jr Am Med. Assoc, 1932, xcix, 1323-1329
- 6 HARRIS, F I, BELL, G H, and BRUNN, H Chronic cicatrizing enteritis Regional enteritis, a new surgical entity, Surg., Gynec, and Obst, 1933, lvi, 637-645
- 7 CARR, P, and BOECK, W C Chronic ulcerative enteritis, Am Jr Digest Dis and Nutr, 1934, i, 161-163

# ACUTE INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ TYPE) \*

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ACUTE infectious polyneuritis is but one of the names of an entity called by others in the past polyneuritis with facial diplegia, acute febrile polyneuritis, motoneuronitis, acute infective neuritis, infective neuronitis, or meningomyeloradiculitis. The term Guillain-Barré syndrome has been used to designate those cases which clinically are characterized by an acute onset, mild or no febrile reaction, radicular neuritis, cranial nerve palsies, muscle tenderness, and which show certain cerebrospinal fluid changes.

The infectious nature of the agent causing this syndrome has not as yet been conclusively demonstrated. Attempts at culture and transmission to animals have been unsuccessful. Aring and Sabin<sup>1</sup> produced no effects in monkeys and mice inoculated with suspensions of tissue from the medulla and pons of a fatal case. The same investigators inoculated mice, guinea pigs, rabbits and rhesus monkeys with the pooled viscera (lungs, liver, spleen, adrenals and kidneys) from three fatal cases with negative results. Cultures of the same material were also non-productive. Honeyman<sup>2</sup> injected directly into the brains of rabbits saline suspensions of spinal cord, brain and peripheral nerves from three fatal cases without result. Despite the failure to transmit the disease or isolate a specific infectious agent, the apparent relationship of the disease to preceding infection in the body has frequently been noted. Upper respiratory tract infections have been especially associated with this entity<sup>3,4</sup>. Foster, Brown and Merritt,<sup>5</sup> in a review of 26 cases of polyneuritis with facial diplegia in a 10 year period at the Boston City Hospital noted that 50 per cent of their cases had a history of preceding upper respiratory infection. A review of seven cases of myeloradiculitis by Strauss and Rabiner<sup>6</sup> similarly emphasized the presence of preceding respiratory tract infection. Sabin and Aring<sup>7</sup> have stated that polyneuritis may be caused by a toxin elaborated by microorganisms of the upper respiratory tract. Garvey, Jones and Warren<sup>8</sup> in describing six cases observed in a two year period following hyperthermia treatments concluded that the disorder was a result of the activation of some infectious agent, perhaps a virus, by the fever. The case histories that follow show that clinically the gastrointestinal tract may be significant as a site of original infection.

Among the polyneuritides encountered in North America, acute infectious polyneuritis is reputedly second in frequency only to alcoholic poly-

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neuritis<sup>9</sup> The association of this entity with military personnel in World War I was noted by Casamajor<sup>10</sup> and by Kennedy,<sup>11</sup> who described cases and autopsy reports among allied troops in France The case reports following have all had their clinical beginnings in India, the first such to be reported to our knowledge Three cases from North Africa, not included in the present report, have also been observed by us

The pathologic studies by Honeyman<sup>2</sup> demonstrated little significant change in the nervous system Kennedy<sup>11</sup> described a patchy neuritis in the peripheral nerves, degeneration of the cells of the anterior and posterior horns of the spinal cord and especially of the cells of the posterior ganglia, and small round cell infiltration around the ganglion and cornual cells Casamajor<sup>10</sup> noted marked degeneration of the nerve fibers within the arachnoid space, most marked in the motor fibers, and increase of cellular neuroglia in the central gray matter, around the root fibers, and in posterior root ganglia Aring and Sabin<sup>1</sup> noted scattered aggregations of lymphocytes and polymorphonuclear leukocytes in the interstitial tissue of the nerves of the cauda equina and comparable changes in the anterior and posterior roots Roseman and Aring<sup>12</sup> noted in their three cases a marked degree of phagocytic reaction in peripheral nerves and its absence centrally Gilpin, Moersch and Kernohan<sup>13</sup> described patchy degeneration of myelin and fragmentation of the axis cylinders of the peripheral nerves without evidence of inflammation Jervis and Strassburger<sup>14</sup> reported a case in which there was degeneration of neuron cells, especially of the ventral horns, and breaking down of myelin sheaths with conspicuous glial reaction The peripheral nerves showed some degenerative changes Sabin and Aring<sup>7</sup> described changes in the adrenals, liver, heart, and kidneys consisting chiefly of focal infiltration with mononuclear cells and small areas of focal necrosis Fitzgerald and Wood's case<sup>3</sup> showed a dense infiltration with lymphocytes and polymorphonuclear leukocytes in one large portal area

The cerebrospinal fluid in patients with the Guillain-Barré syndrome is characterized by "albumino-cytologic dissociation"—an increased total protein with slight or no cellular response During the progressive, earlier phases of the disease the cerebrospinal fluid pressure may be considerably elevated Ford and Walsh<sup>15</sup> reported a patient in whom decompression was done to save the patient's vision which was threatened by a progressive papilledema The elevation of total protein in the spinal fluid may reach tremendous proportions Bassoe<sup>16</sup> reported a total protein of 6,660 mg per cent in a three and a half year old girl who subsequently recovered The average range of values for total proteins, however, is considerably lower Guillain<sup>17</sup> inferred that levels below 400 mg per cent are indicative of abortive cases, but clinical experience generally in this country does not support that thesis In many instances the determination of cerebrospinal fluid protein is not made at the height of the disease when the highest level is anticipated, because the importance diagnostically of this test is not recognized or because facilities are not available for its performance

Mortality figures vary greatly. Guillain<sup>17</sup> predicated that all cases recover. Foster, Brown, and Merritt,<sup>5</sup> however, reported a 42 per cent mortality in their group, whereas Roseman and Aring's<sup>12</sup> review of 16 cases showed a mortality of 18.8 per cent.

This syndrome must be distinguished from other infectious diseases of the central nervous system as well as other types of polyneuritis. The chief entities to be differentiated are acute anterior poliomyelitis and diphtheritic polyneuritis. De Sanctis and Green<sup>18</sup> have elaborated on the problem of the differential diagnosis of acute anterior poliomyelitis and the Guillain-Barré syndrome. Progressive involvement, sensory changes, symmetrical ascending paralysis, and albumino-cytologic dissociation in the cerebrospinal fluid favor the diagnosis of the Guillain-Barré syndrome. Diphtheritic polyneuritis may be ruled out by the presence of a positive Schick test, the failure to find the pathogenic bacteria in nasopharyngeal smears and culture, and the absence of clinical signs and symptoms of diphtheria.

#### CASE REPORTS

*Case 1* This 37 year old patient had been stationed in Karachi, India, when he noted on January 26, 1944 a "tired feeling" in both legs, numbness in the fingers and toes, and occipital headaches. During the next month the patient found it difficult to enter and leave his plane because of weakness in lower limbs, for a period of three days in mid-February he was aware of diplopia. On February 26, 1944 he was admitted to a Station Hospital where temperature, pulse, and respirations were found to be normal. Spinal fluid examination showed 1 white blood cell, 189 red blood cells, and Pandy slightly positive on March 6, 1944. Weakness in the lower limbs meanwhile became progressively worse, the patient now experienced difficulty in rising from a squatting position and could hardly walk forward or backward. By March 20, 1944, upon transfer to another station hospital, the patient required the aid of a cane in walking. On March 22, 1944 diplopia returned and persisted thereafter. Deep tendon reflexes were absent throughout, vibratory sensation was lost in both feet. Spinal fluid on March 22, 1944 showed initial pressure of 130 mm of water, 1 white blood cell, positive Ross Jones test, colloidal gold 2210000000, and negative Kahn reaction. On April 23, 1944 the patient reached the Army Air Forces Regional Hospital No 1, Coral Gables, Florida. At that time he could not stand unsupported and was quite tender over most of the muscles of the extremities. Deep tendon reflexes were absent throughout and vibratory sensation was absent from the level of the iliac crests downward. Mild diffuse weakness of the upper extremities with atrophy of most muscle groups of all extremities was present. On April 24, 1944 spinal fluid was under pressure of 235 mm water, showed no white blood cells, a positive Pandy, total protein of 344 mg per cent, and colloidal gold 35533420. The patient remained afebrile, complained bitterly of severe frontal headaches which on occasion were relieved by intramuscular injections of ergotamine tartrate. Despite repeated transfusions, supplemental feedings, high vitamin intake, parenteral infusions, the patient became progressively worse in that the level of severe muscle weakness continued to rise. On May 18, 1944 the patient was started on hot pack therapy to the extremities and back, but this was discontinued by May 29, 1944 because the tempo of progression appeared to hasten. By this time the patient was unable to rise or turn in bed and exhibited mild nuchal rigidity. Sense of position, vibratory sense, and stereognostic sense were lost in all extremities. The spinal fluid on May 27, 1944

showed an initial pressure of 275 mm water, no white blood cells, 585 mg per cent total protein, and colloidal gold curve of 1232334432. Spinal fluid was mildly xanthochromic at this time. Transfusions and intravenous infusions were now necessary to maintain adequate fluid intake. Lumbar puncture on June 14, 1944 showed a xanthochromic fluid under 210 mm water pressure, no white blood cells, 732 mg per cent total protein, and colloidal gold 3455554443. During the last week of June, the patient complained of recurrent transient episodes of difficulty in swallowing so that he refused all but small amounts of liquids by mouth. On July 19, 1944 the spinal fluid was intensely xanthochromic, showed 2 white blood cells per cu mm, and total protein of 233 mg per cent. Twelve hours later the patient went into acute respiratory failure, he suddenly became cold and cyanotic, and respirations were rapid, shallow and gasping. He complained of pain in the lower chest on both sides, but remained afebrile and had no cough. He was placed in an oxygen tent for several hours and then placed in a respirator. For the next eight days he remained in the respirator, being repeatedly transfused and receiving parenteral fluids. At the end of this time he was able to breathe satisfactorily again. Appetite improved thereafter and headaches decreased in frequency. In mid-August 1944 he began to complain of episodes of haziness of vision. Eye consultant noted two to three diopters of papilledema of both discs, with swollen veins and numerous scattered, large, flame-shaped hemorrhages. Symptomatically no great change occurred thereafter except for a transient episode of breathlessness, relieved by a 24 hour stay in an oxygen tent on September 11, 1944. The last spinal fluid examination was done on August 28, 1944, at which time the fluid was decidedly less xanthochromic than on previous occasions, initial pressure was 350 mm water, there were no white blood cells, total protein was 815 mg per cent, and colloidal gold was 0012212333. The patient was eating well and was able to sit up in a wheel chair.

*Case 2* This 35 year old enlisted man was stationed in North Central India when, on February 28, 1944, he noticed a "fullness" in his abdomen and vomited. No chills, fever, diarrhea, muscular aches or other pains were present. On March 2, 1944 he developed a "sore throat". A week later he was admitted to a Station Hospital because of persistent headache, neckache, generalized muscle soreness, and regurgitation of fluids through his nose. On admission, oral temperature of 99.6° F was noted, the uvula was found to deviate to the left, the right half of the pharynx, the soft palate, and the tongue were relatively insensitive to touch. Transient diplopia and vertigo were present on March 11. Complete blood count, urinalysis, blood smears for malaria, and nasopharyngeal smears for diphtheria were negative. On March 13 the patient was transferred to a General Hospital where the spinal fluid on the next day was found to contain 38 cells (95 per cent lymphocytes, 5 per cent endothelial cells) and a total protein of 83 mg per cent. Colloidal gold and Kahn reaction on the cerebrospinal fluid were normal. Nasal speech, regurgitation of fluids through the nose, and absence of triceps, abdominal and left Achilles tendon reflexes were noted. Severe back pains were present on March 15, hot packs were applied three times daily to the chest, back, neck, and lower extremities for the following two weeks. By March 17 the low grade fever had returned to normal level. Repeat spinal fluid examination on April 8 showed 5 cells, total protein 125 mg per cent, and a 2 globulin. Hypesthesia of the lateral surface of the right thigh, and return of the abdominal skin reflexes were now evident. Continued mild improvement persisted, but on May 16, 1944, at time of transfer to Army Air Forces Regional Hospital No. 1, he still showed moderate weight loss, slight dragging motion in the left lower extremity, small area of hypesthesia to touch and pinprick over right lateral thigh absent Achilles reflexes bilaterally, and moderate difficulty in swallowing solid foods. Sedimentation rate, complete blood count, and urinalyses were normal. Swallowing function test on May 23, 1944 showed marked retention of barium in vallecula and

reflexes, frequent stumbling on attempts to walk, hypesthesia to touch of both hands and feet. Intensive parenteral and oral vitamin B and multivitamin therapy did not alter the patient's status greatly by June 12, when he was transferred to another Station Hospital. On arrival here he complained of severe aching pains in both shoulders. Examination disclosed weakness in the grip of both hands, hypesthesia to touch and pain over both hands, partial paralysis of both external recti muscles, and winging of the right scapula. Spinal fluid examination on June 24, 1944 showed no white blood cells, positive Pandy (total protein could not be done), and negative Kahn reaction. Under physiotherapy and high vitamin therapy, weakness and hypesthesia of the hands receded. He was evacuated to this country and reached the Army Air Forces Regional Hospital No 1 on August 2, 1944 where examination revealed marked winging of the right scapula, absent biceps, quadriceps and Achilles tendon reflexes, diplopia, and mild hypesthesia to touch and pain over the medial aspect of the left leg. Spinal fluid examination on August 10, 1944 revealed initial pressure of 160 mm water, 7 lymphocytes per cu mm, slightly positive Pandy, total protein 41 mg. per cent, colloidal gold 00011110000, and negative Wassermann reaction. The patient left the hospital on emergency furlough on August 14, 1944.

### CONCLUSIONS

Six cases of acute infectious polyneuritis of the Guillain-Barré type with clinical onset in India are reported. Preceding gastrointestinal tract disease was noted in four cases and may be related to the onset of neurologic symptoms. The fact that many of these cases were primarily diagnosed as acute anterior poliomyelitis seems worthy of notation. The differentiation from acute anterior poliomyelitis can be made chiefly on the findings of albuminocytologic dissociation of the cerebrospinal fluid.

### BIBLIOGRAPHY

1. ARING, C D, and SABIN, A B. Fatal infectious polyneuritis in childhood, *Arch Neurol and Psychiat*, 1942, *xvii*, 938-942.
2. HONEYMAN, W M. Pathological study of a group of cases sometimes referred to as polyneuritis, *Bull Neurol Inst New York*, 1937, *vi*, 519.
3. FITZGERALD, P J, and WOOD, H. Acute ascending paralysis (Guillain-Barré syndrome), *U S Nav Bull*, 1944, *xliii*, 4.
4. STEARNS, A W, and HARRIS, H I. Infectious polyneuritis, *U S Nav Bull*, 1944, *xliii*, 13.
5. FOSTER, F M, BROWN, M, and MERRITT, H H. Polyneuritis with facial diplegia, *New England Jr Med*, 1941, *ccxv*, 51-56.
6. STRAUSS, I, and RABINER, A M. Myeloradiculitis, *Arch Neurol and Psychiat*, 1930, *xxiii*, 240.
7. SABIN, A B, and ARING, C D. Visceral lesions in infectious polyneuritis, *Am Jr Path*, 1941, *xvii*, 469-482.
8. GARVEY, P H, JONES, N, and WARREN, S L. Polyradiculoneuritis, *Jr Am Med Assoc*, 1940, *cxv*, 1955.
9. BROWN, M R. Diagnosis and treatment of polyneuritis, *Med Clin N Am*, 1938, *xxii*, 627.
10. CASAMAJOR, L. Acute ascending paralysis among troops, *Arch Neurol and Psychiat*, 1919, *ii*, 605.
11. KENNEDY, FOSTER. Infectious neuronitis, *Arch Neurol and Psychiat*, 1919, *ii*, 621.
12. ROSEMAN, E, and ARING, C D. Infectious polyneuritis, *Medicine*, 1941, *xx*, 463.





# CASE REPORTS

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## ISOLATED (FIEDLER'S) MYOCARDITIS: REPORT OF CASE FIRST MANIFESTED BY ARTERIAL EMBOLI IN EX- TREMITIES AND TERMINALLY BY MURAL THROMBI IN THREE OF THE HEART CHAMBERS \*

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ACUTE isolated myocarditis was first described in 1900 by Fiedler<sup>1</sup>. It is a rare disease and one in which inflammation of the myocardium is apparently the only important acute lesion in the body. Engelhardt and Bruno,<sup>2</sup> in a recent review of the literature, collected nine cases from the American and 46 additional cases from the world literature. Various infections have been suspected as causing this disease such as acute upper respiratory infections, influenza, pneumonia, measles, virus infections, syphilis, also toxins have been suggested as etiologic agents circulating in the blood stream from diphtheria or streptococcus infections. Likewise implicated are vitamin B deficiency states, an allergic reaction or idiosyncrasy to bismuth, arsenic, sulfur, sulfonamides, alcohol, sparteine and adrenalin. Pregnancy, burns and hyperthyroidism have been associated respectively with certain cases. It seems safe to state at present that there is really no known cause, although recently Helwig and Schmidt<sup>3</sup> have described "a filter-passing agent producing myocarditis in anthropoid apes and small animals" obtained from hydrothorax fluid of a gibbon which dropped dead, and hydrothorax fluid and spleen of a chimpanzee dying very suddenly.

Grossly both animals had dilated hearts, pericardial effusion, pulmonary edema and bilateral hydrothorax and histologically pulmonary edema and an intense diffuse interstitial myocarditis "strikingly similar" to that in human acute interstitial myocarditis of unknown etiology.

The filter-passing agent was passed through a series of 122 mice, and with rare exception regularly produced paralysis followed by death or apparent recovery after a week or two. At necropsy interstitial myocarditis was found in almost all the animals. In some it was very severe, in others limited to small foci of necrosis and inflammation. The agent produces myocarditis in guinea pigs and rabbits, also. It is potent and specific when introduced intravenously, intraperitoneally, subcutaneously, intracranially, and by nasal instillations, and is present in the nasal washings of inoculated animals. It is destroyed by heating to 70° C for 20 minutes, but withstands heating to 56° C for 20 minutes, losing some of its potency, but not its specificity. It passes Berkefeld and Seitz filters. Such an agent has not been previously described, and strongly suggests that isolated myocarditis of humans may well also be a virus disease.

\* Received for publication October 16, 1944

Clinically, the most striking manifestations in humans are progressive myocardial weakness with dyspnea, precordial pain, tachycardia, cyanosis, low blood pressure and increase in the size of the heart. Most of the reported electrocardiograms have shown either prolonged PR or QRS intervals with inverted T-waves in one or more leads. Any combination of these abnormalities may be encountered. It occurs at any age, but is more frequent in young people. Some patients die suddenly, others have a protracted course extending for several months even up to two years. It is most frequently mistaken for coronary thrombosis, pericarditis or acute rheumatic myocarditis. The clinical diagnosis is made by exclusion. In a young person with a history of rapid, progressive myocardial insufficiency, the exclusion of the ordinary etiological factors, especially rheumatic fever, should lead one to consider acute isolated myocarditis as the clinical diagnosis.

Recently, we observed a case with this disease whose first symptoms were those of emboli to the left brachial and right popliteal arteries. These manifestations emphasize the observations previously described that the disease process may be present for a considerable time before symptoms appear. The patient's course was one of progressive myocardial insufficiency and death. At autopsy, there were large antemortem thrombi in three chambers of the heart. Microscopic examination of the myocardium revealed the characteristic lesions of this disease. Because of the rarity of the lesion and the unusual features of this case, we considered it worthwhile to add it to those previously reported.

#### CASE REPORT

The patient was a 25 year old, male Negro. There was no past history of rheumatic fever, chorea, diphtheria, scarlet fever, influenza, syphilis or hypertension. He had not taken any drug and had been eating an adequate diet. He was well until July 30, 1943. On that date, immediately after jumping out of a truck, he experienced sudden, severe pain and tenderness along the medial aspect of his left forearm with marked weakness of the corresponding hand. He was seen by a medical officer who described the left forearm and hand as "cool, pale with absent radial and ulnar pulsations." A diagnosis of thrombosis of the left subclavian artery was made. He was treated with rest, morphine, aminophyllin and warm wet dressings to the arm. The pain gradually subsided in two weeks and strength slowly returned to the arm, but the hand remained weak. Arterial pulsations continued to be absent. While still in the hospital, during convalescence, he awakened August 15, 1943 with a sharp pain in the right popliteal region. The pain extended rapidly to involve the whole right lower leg. The extremity became cold and arterial pulsations were absent. The severe pain subsided gradually over several days, but the leg continued to ache constantly and motor power in the right leg was very weak. During the latter part of August he had a severe attack of substernal pressure pain for eight hours. On September 16, 1943 there was a recurrence of substernal pain for several hours. The patient was admitted to this hospital on October 1, 1943. His complaints on admission were constant aching pain and weakness of the right lower leg and slight weakness of the left hand.

Upon physical examination, his blood pressure was 122 mm Hg systolic and 86 mm diastolic, temperature 98° F, pulse 84, and respirations 18. The heart was at the upper limits of normal size. No cardiac murmurs were heard. The left radial, ulnar, brachial and the right dorsalis pedis, anterior and posterior tibial and popliteal pulses were absent. Grip of the left hand was weak. There was weakness of the

right lower leg and it was cool to touch. An electrocardiogram (figure 1) showed rounded and inverted T-waves in all leads with a deep  $Q_1$  and  $2$ .  $P_2$  and  $3$  measured 6 and 5 mm respectively. The heart size was normal by chest roentgenogram (figure 2). There was a sedimentation rate of 30 mm (Westergren method). The urine

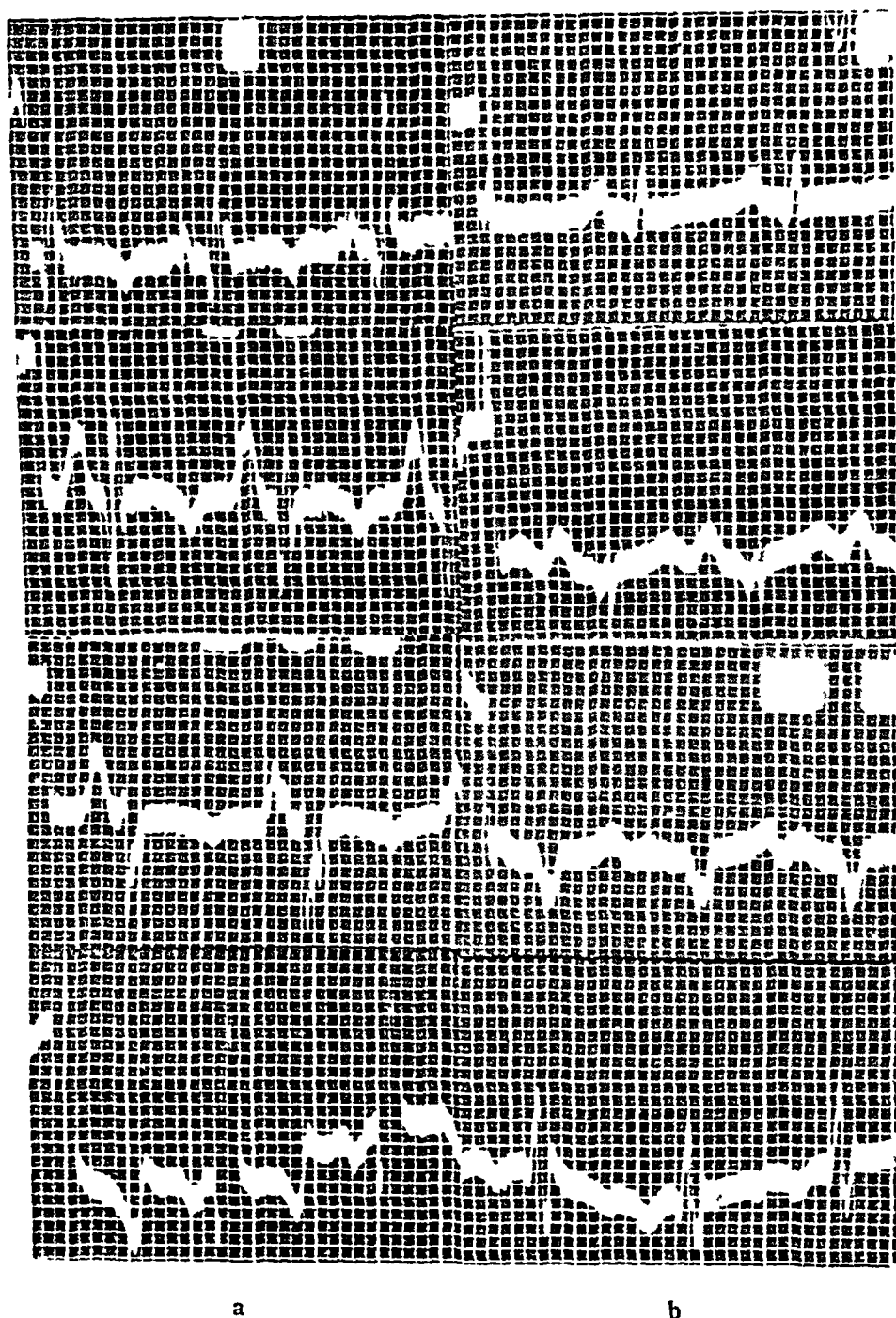


FIG 1 a Taken October 4, 1943, shows deep  $Q_1$  : with rounded and inverted T-waves in all leads. P-waves in Leads II and III are very prominent, indicating auricular hypertrophy. b Taken December 4, 1943, shows a low electromotive force.  $Q_1$  and  $2$  are still present.  $T_1$  and  $4$  are now diphasic.

was normal, the Kahn reaction negative, hematocrit 41 per cent, and the prothrombin time 22 seconds. A blood culture was negative.

The patient was treated with bed rest and aminophyllin 0.3 gm t.i.d. He was given gradually increasing positive and negative Paevex treatments to the right lower leg from October 11 to November 15, 1943, until he received a positive pressure of 20 and a negative pressure of 80 for two hours daily. On this régime he had gradually decreasing pain and increased strength in the right leg. On October 26 he complained of mild dyspnea while in bed and a gallop rhythm was first audible at the apex. A right deep femoral phlebitis was evident on November 18 and on the same

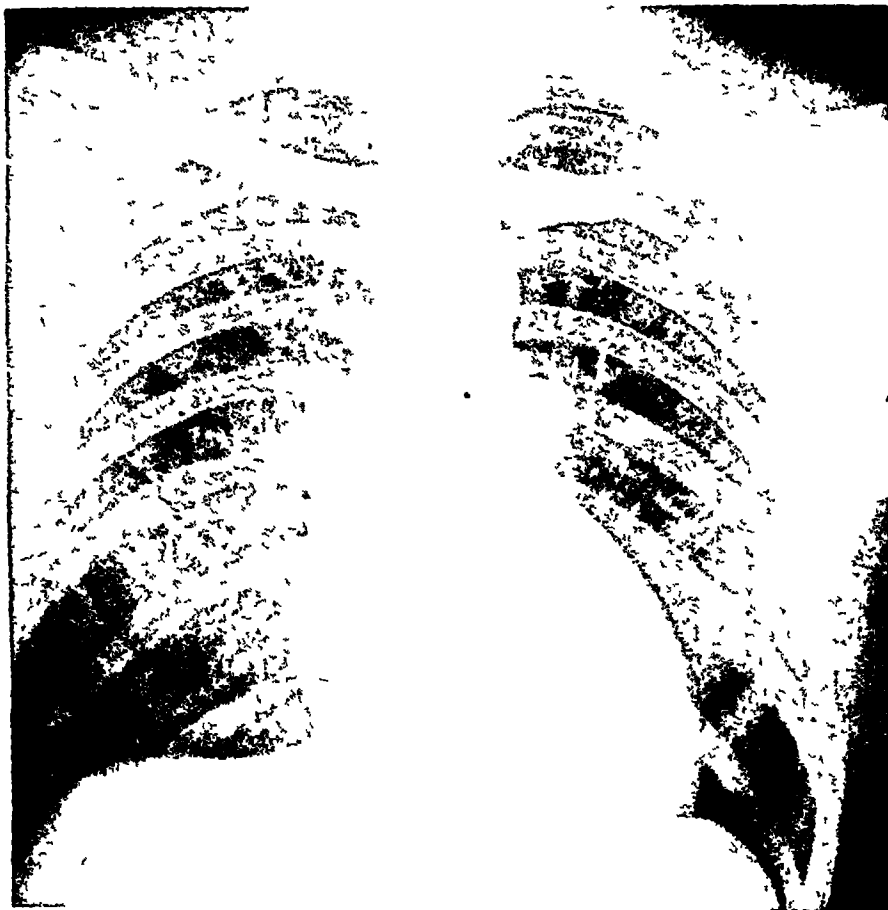


FIG 2 Six foot chest roentgenogram taken October 4, 1943, shows the heart shadow at the upper limits of normal size.

day he had a pulmonary infarct with hemoptysis. The right femoral vein was immediately explored. The vein and surrounding tissues were acutely inflamed and the superficial femoral vein was completely occluded by an organized thrombus which extended upward into the common femoral vein and laterally into the profunda femoris. The clot was aspirated and the superficial femoral vein was ligated and cut. Following this episode the patient had fever from 99.6° to 102° F daily until his death. He also complained of dyspnea at rest and the gallop rhythm became more prominent. Hemoptysis and physical signs of pulmonary infarction gradually subsided. On November 19, 1943 the patient noted severe right lower quadrant pain.

with voluntary spasm and marked tenderness in the right lower quadrant. White blood cells numbered 18,100. It was thought that the patient probably had a right iliac phlebitis. However, because of the possibility of an acute appendicitis, an exploratory operation was done. A normal appendix was removed and the right iliac vein was explored, but no thrombus was palpable. The patient had relief of his right lower quadrant pain after this procedure. Another pulmonary infarction occurred on November 21, 1943, following which the heart became moderately enlarged and signs of heart failure, dyspnea, tachycardia, gallop rhythm and bifid apex impulse were evident. On December 4, 1943 the patient had an attack of severe substernal pain which lasted several hours. Following this, he became very drowsy and

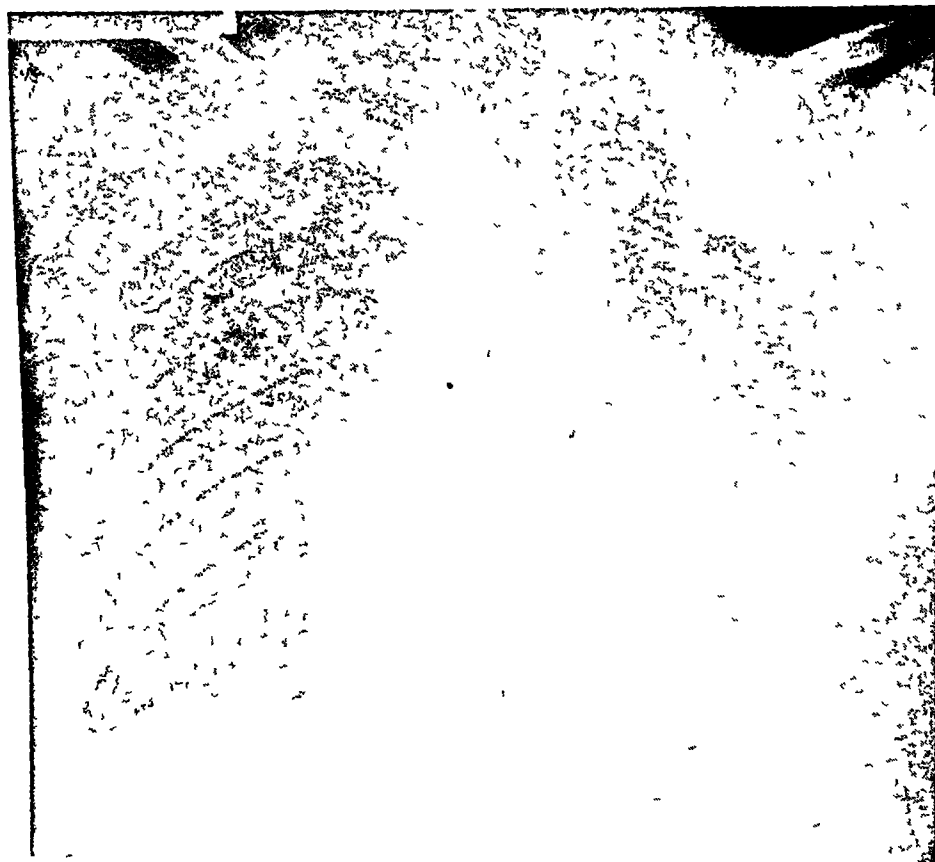


FIG 3 Portable chest roentgenogram taken December 5, 1943, shows a marked increase in the cardiac shadow with the left border of the heart shadow extending to the left thoracic cage

orthopneic. Moist râles were heard at both lung bases, the liver became palpable, and ankle edema appeared. The patient was rapidly digitalized without improvement. The signs of heart failure increased rapidly (figure 3). The blood non-protein nitrogen rose to 107. He died in his sleep on December 8, 1943.

**Autopsy Findings** The external examination of the body was normal except for slight pitting edema of the right ankle. The heart weighed 610 gm. The epicardium was smooth and glistening. The chambers were all moderately dilated. Multiple rubbery, fairly firm, yellowish-red to dark bluish-red, firmly adherent thrombi were present in the right auricle, right ventricle and left ventricle (figures 4 and 5). The valve leaflets were smooth and delicate. The left ventricle varied in thickness

from 1.5 cm to 0.7 cm. The right ventricle averaged 0.6 cm. The myocardium was of peculiar yellowish, beefy-red color, and firm. No areas of old or recent infarction were recognized grossly. The coronary arteries were widely patent and lined by smooth, glistening intima. The aorta measured 4 cm in circumference at the level of the diaphragm, and was of normal elasticity. The intima was smooth except for an occasional small bright yellow atheromatous nodule. The inferior vena cava contained a large, bluish-red, free lying thrombus extending to 6 cm above the bifur-



FIG 4. Shows mural endocardial thrombi in right auricle and ventricle

cation. It was firmly attached to the intima at the left of the bifurcation and it continued inferiorly with a large thrombus which completely occluded the lumina of the common iliac veins, extending distally in the left for a distance of 3 cm, and in the right throughout the right common iliac vein and femoral vein to the fossa ovalis, where the vein had been ligated by black silk sutures and a 2 cm segment of the vein removed. The thrombus continued distally from the point of ligation down to the level of the mid-calf. After the body was embalmed the left brachial and the right femoral arteries and their branches were opened and examined to the wrist and ankle,

respectively. There was a small amount of material grossly resembling fibrin adherent to the wall of the brachial artery in its midportion (microscopic examination disclosed this as a completely organized thrombus and contracted residuum of a previous thrombus or embolus, see below) the right femoral system contained recent partially organizing clot. The posterior tibial artery was filled with a dark bluish-red thrombus.

The lungs were atelectatic in the lower portions, and contained small recent pulmonary infarcts. The small arteries leading to these contained adherent thrombi. Gross examinations of the intestinal tract, pancreas, spleen, liver, gall-bladder and adrenals were essentially negative. The kidneys contained multiple slightly depressed

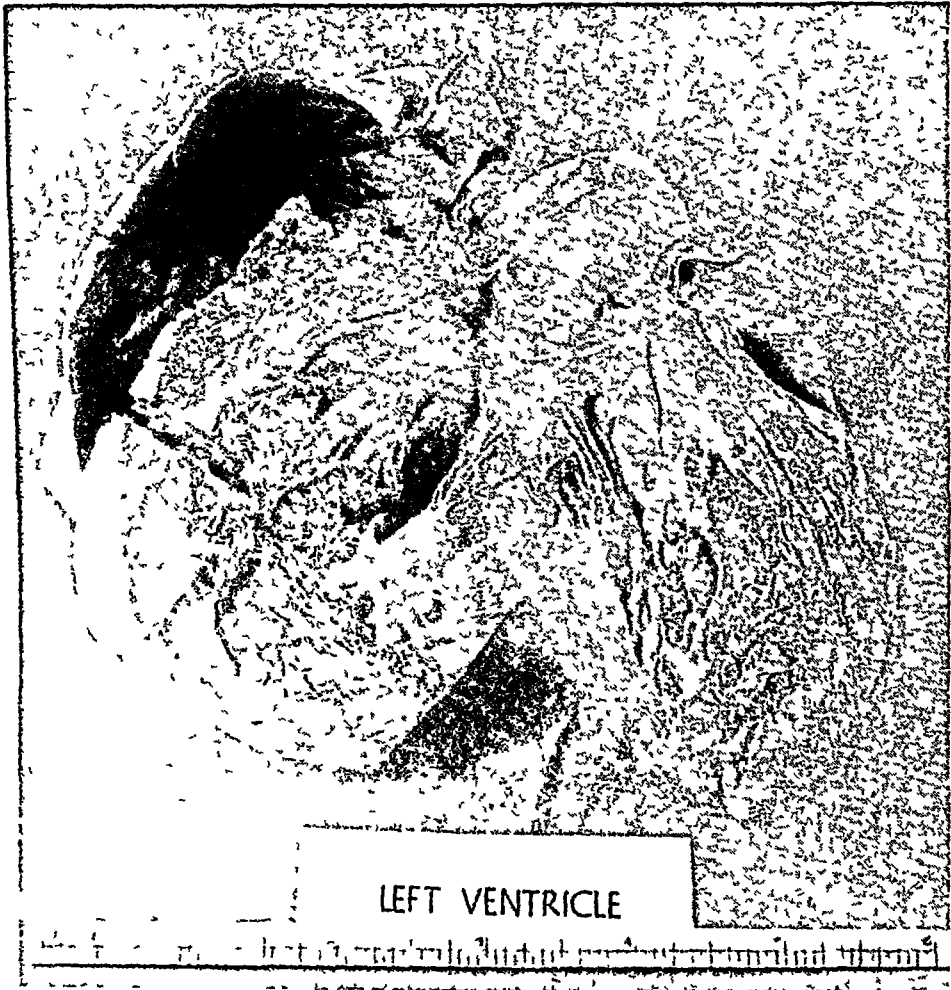


FIG 5 Shows mural endocardial thrombi in the left ventricle

infarcts in the lower pole of the left kidney and a small infarct in the midportion of the right kidney. The remainder of the genitourinary tract was grossly normal. The brain and spinal cord were normal. The muscular, osseous, lymphoid and endocrine systems were normal.

On microscopic examination the conspicuous pathological changes were found to be limited to the heart and vascular system. The myocardium exhibited extensive interstitial collagenous connective tissue deposition with occasional small foci of lymphocytes and other monocytes, together with a few plasma cells and scattered polymorphonuclear leukocytes (figure 6). The individual myocardial fibers show



FIG 6 Interstitial fibrosis and cellular infiltration, with hypertrophy of cardiac muscle  $\times 180$



marked, and often irregular hypertrophy, with extensive vacuolization in many fields. The mural thrombi showed partial organization immediately adjacent to the endocardium, primarily in the areas where the myocardial fibrosis had extended to the subendocardium. There were organizing thrombi in both iliac veins. The left ulnar artery contained several small completely organized polypoid thrombi which were firmly attached to the intima though these were contracted, and did not materially decrease the size of the lumen. The left brachial artery contained a similar completely organized thrombus. This, too, was contracted, so that it affected lumen volume little, if at all. The right posterior tibial artery contained a large laminated thrombus which was slightly organized at the periphery. Sections of the lung revealed multiple recent, old and organizing infarcts, and chronic passive congestion. Sections of the kidneys confirmed the gross impression of multiple ischemic infarcts with marked passive congestion, with adjacent arteries occluded by organizing thrombi. The reaction of repair and inflammation about these infarcts was surprisingly slight. Microscopic sections of the stomach, small intestines, spleen, pancreas, gall-bladder, adrenals, bladder, prostate, seminal vesicles, testes, endocrine glands, brain, bone, muscles, lymph nodes and breasts were essentially normal. The principal anatomic diagnoses were

- 1 Myocardial fibrosis (Fiedler's myocarditis) with focal endocardial fibrosis
- 2 Cardiac hypertrophy and dilatation
- 3 Mural thrombi, multiple, partially organized, right auricle, right ventricle, and left ventricle
- 4 Emboli, multiple, of left brachial artery (organized and recanalized, not occluding), of radial and ulnar arteries (organized and recanalized, not occluding), of right popliteal and posterior tibial artery (recent and partially organized), of small branches of the pulmonary artery (old, organizing and recent), and of renal arteries (partially organized)
- 5 Ligation and resection of 2 cm of the right posterior femoral vein
- 6 Thrombi (recent) of vena cava, common iliac veins, right popliteal, and right posterior tibial veins
- 7 Pulmonary infarction, multiple (recent and old)
- 8 Renal infarcts, multiple, ischemic, bilateral, small

### SUMMARY

A case of isolated myocarditis of the Fiedler's type is presented. The first signs of the disease were emboli to the left brachial and right popliteal arteries. The course was one of progressive myocardial failure with chest pain, dyspnea, tachycardia, gallop rhythm and rapidly enlarging heart. The clinical diagnosis was myocardial infarction with mural endocardial thrombi resulting in peripheral emboli. Only after microscopic examination of the heart was the true nature of the condition established.

### BIBLIOGRAPHY

- 1 FIEDLER, A. Über akute interstitielle Myokarditis, *Centralbl f inn Med*, 1900, cci, 212
- 2 ENGELHARDT, H. T., and BRUNO, F. E. Fiedler's myocarditis, *New England Jr Med*, 1943, cclxxxviii, 222-224
- 3 HELWIG, F. C., and SCHMIDT, E. C. H. A filter-passing agent producing interstitial myocarditis in anthropoid apes and small animals, *Science*, 1945, cii, 31-33

## THE COMBINATION OF HYPERTHYROIDISM AND PERNICIOUS ANEMIA REPORT OF A CASE WITH A REVIEW OF THE LITERATURE\*

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IN the earlier literature on hyperthyroidism, anemia was regarded as one of the characteristic findings. From the reports, it is apparent that the diagnosis was usually made from the color of the face. Later on, when exact blood studies were performed, it was found that not only were the signs of anemia missing, but also that an increase in the number of red cells might actually be present in some instances. Kochei<sup>1</sup> was the first to stress this.

The relatively normal erythrocyte and hemoglobin values are emphasized by the data of several workers. In 678 cases of hyperthyroidism, Plummer<sup>2</sup> found an average of 4.79 million erythrocytes per cu mm with a hemoglobin of 83.1 per cent, Jackson<sup>3</sup> obtained an average of 4.79 million red cells and a hemoglobin of 78 per cent, and McCullagh and Dunlap<sup>4</sup> in 1200 cases noted an average of 4.55 million red cells with a hemoglobin of 82.5 per cent. In 20 cases reported by Wahlberg<sup>5</sup> the red cells ranged between 3.45 and 4.43 million (average 4.069) and the hemoglobin between 70 per cent and 80 per cent (average 75.5). The figures are somewhat higher in Deutsch's<sup>6</sup> cases: 3.3 to 5.5 million erythrocytes and 77 per cent to 102 per cent hemoglobin.

In fact some observers have noted an increase in the number of red blood cells. Zimmermann<sup>7</sup> examined 24 males and 76 females, in seven the erythrocyte count was below 4.0 million, in 27 it was above 5.0 million, in five above 5.5 million, and in one, more than 6.0 million. He noted no relationship between the blood count and the severity or duration of the disease. A very definite increase in red blood cells was reported by Schwanke,<sup>8</sup> who observed an erythrocyte count as high as 8.6 million. Blank<sup>9</sup> described poikilocytosis, sometimes combined with basophilic stippling, in 30 per cent of 17 patients with Graves' disease.

In some recent publications, the morphological blood picture in hyperthyroidism is often described as normal. Joll<sup>10</sup> states that the red cells are "seldom much altered," and that only in advanced cases does one find poikilocytosis, polychromatophilia, and basophilic stippling. Means<sup>11</sup> says there is no characteristic change, as do Lawrence and Rowe<sup>12</sup>. According to Crotti,<sup>13</sup> Fleischhans,<sup>14</sup> and Kleiner and Renyi-Vamos,<sup>15</sup> the blood picture exhibits deviations from the normal only in severe cases, when the findings are those of a secondary anemia. Our own findings in a series of cases of hyperthyroidism and hypothyroidism (table 1) reveal no striking or characteristic changes in the blood pattern.

Although the theory has been advanced that the thyroid stimulates hematopoiesis,<sup>16</sup> the combination of polycythemia and hyperthyroidism is infrequent. A search of the literature reveals that only nine cases have been reported<sup>17, 18, 19, 20, 21, 22, 23</sup>, the diagnoses in five of these are questionable. We have observed this combination on one occasion.

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TABLE I

Correlation of Data in 20 Patients with Hyperthyroidism and 25 with Hypothyroidism<sup>1</sup>

|                                 | Hyperfunction |                   | Hypofunction |         |
|---------------------------------|---------------|-------------------|--------------|---------|
|                                 | Range         | Average           | Range        | Average |
| Age (years)                     | 21-50         | 36.2              | 14-65        | 34.2    |
| B M R (%)                       | +10-+72       | 31.2 <sup>2</sup> | -4--22       | -13.23  |
| Hemoglobin (%)                  | 54-115        | 78.7              | 60-100       | 79.7    |
| No. of red cells<br>(per cu mm) | 3.45-6.5      | 4.274             | 3.5-5.2      | 4.387   |
| Color index                     | 0.65-1.15     | 0.944             | 0.9-1.1      | 0.96    |

<sup>1</sup> Two cases of hyperthyroidism are not included in this summary. The one case was probably connected with a pernicious anemia. However, a thorough study could not be made. The other patient suffered from a polycythemia.

<sup>2</sup> Not including two cases with b m r of +4.2 and +4.0, respectively (after operation).

A profound anemia, even pernicious anemia, is more likely to be seen in combination with frank myxedema than with hyperthyroidism. As Means, Castle, and Lerman<sup>24</sup> remark, "That pernicious anemia may resemble myxedema, and that myxedema may resemble pernicious anemia, has long been apparent."

In view of the above, the coexistence of hyperthyroidism and pernicious anemia is quite remarkable. Handbooks on endocrinology and hematology either do not mention the combination at all, or only to say that they have not observed it. Youmans,<sup>25</sup> for example, writes that "in parts of the country where both diseases occur frequently, their combination is not seen."

On the other hand, 28 authors have reported this combination in 75 instances (table 2). In some of these cases, however, the diagnosis of pernicious anemia seems not to have been fully established, e.g., Schaumann and Saltzmann<sup>26</sup> question the diagnosis in Kerppola's cases<sup>27</sup>. Some reports of the combination may have escaped our notice because of the title under which published, whereas a number of others undoubtedly have never been reported at all. Apparently Suzman<sup>28</sup> saw the two conditions together, for, on reporting the basal metabolism in pernicious anemia, he states that cases with a thyroid condition are not included. Davidson and Gulland<sup>29</sup> mentioned patients with pernicious anemia following exophthalmic goiter, but gave no details. Meulengracht<sup>30</sup> claimed his attention had not been drawn to this problem in the beginning of his study. The same conclusion can be drawn from Stenstam's publication<sup>31</sup>. In his records, both diseases occurred together three times in a series of 192 cases of pernicious anemia observed between 1929 and 1938, but among the cases admitted to the hospital in 1938 alone, he found the coincidence four times.

Of the 75 cases listed in table 2, a total of 50 was reported by six authors,<sup>30, 31, 32, 33, 34, 35</sup> and the remainder by 22 examiners.

The occurrence of other diseases in the course of pernicious anemia is not infrequent. One hundred eight (17.2 per cent) of Giffin and Bowler's<sup>36</sup> 628 patients with pernicious anemia suffered also from other diseases. Wilkinson<sup>34</sup> saw concomitant maladies in 98 (26.4 per cent) of 370 patients. Of these, endocrine disorders were the third most frequent, and of the endocrine patients five had exophthalmic goiter, one hyperthyroidism, and three myxedema.

TABLE II

Data in All Reported Cases of the Combination of Hyperthyroidism and Pernicious Anemia

| Author                                     | No instances of combination of P A & H | Sex | Age  | Total No Cases |      | Order of Onset |         |        |
|--|--|-----|------|----------------|------|----------------|---------|--------|
|  |  |     |      | P A            | H    | P A first      | H first | Simult |
| Adler <sup>71</sup>                        | 2                                      | f   | 51   | 430            | 1180 | .              | +       |        |
| Aitoff and Loewy <sup>78</sup>             | 1                                      | f   | 44   |                |      |                | +       |        |
| Andrus and Wintrobe <sup>32</sup>          | 5                                      | m   | 54   |                |      | +              |         |        |
|  |  | f   | 31   |                |      | +              |         |        |
|  |  | f   | 43   |                |      | +              |         |        |
|  |  | f   | 47   |                |      | +              |         |        |
|  |  | f   | 61   |                |      |                |         | +      |
| Bauer <sup>79</sup>                        | 1                                      | f   | 49   | 20             |      |                | +       |        |
| Billings <sup>80</sup>                     | 1                                      | f   | 36   |                |      |                |         | +      |
| Burwell, Smith and Neighbors <sup>25</sup> | 1                                      | m   | 23   |                |      |                | +       |        |
| Faber <sup>81</sup>                        | 1                                      |     |      |                |      |                | +       |        |
| Fernandez <sup>82</sup>                    | 1                                      | m   | 15   |                |      |                |         | +      |
| Fleischhans <sup>14</sup>                  | 1                                      |     |      | 628            |      | +              |         |        |
| Giffin and Bowler <sup>33</sup>            | 5                                      |     |      |                |      |                |         |        |
| Gulland and Goodall <sup>72</sup>          | 2                                      | f   | 25   |                |      |                | +       |        |
|  |  | f   | 45   |                |      |                | +       |        |
| Hansen <sup>77</sup>                       | 1                                      | f   | 30   |                |      |                | +       |        |
| Hanssen and Stub <sup>83</sup>             | 1                                      |     | 35   |                |      |                | +       |        |
| Heeres <sup>84</sup>                       | 1                                      |     |      |                |      |                | +       |        |
| Kerppola <sup>27</sup>                     | 2                                      | f   | 30   |                |      |                | +       |        |
|  |  | f   | 37   |                |      |                | +       |        |
| Landstrom <sup>55</sup>                    | 1                                      |     |      | 114            |      |                |         |        |
| Lichtenstein <sup>46</sup>                 | 1                                      | f   |      |                |      |                |         | +      |
| Meulengracht <sup>30</sup>                 | 8                                      | f   | 30   | 151            |      |                | +       |        |
|  |  | f   | 30   |                |      |                | +       |        |
|  |  | f   | 35   |                |      |                | +       |        |
|  |  | f   | 39   |                |      |                | +       |        |
|  |  | f   | 53   |                |      |                | +       |        |
|  |  | f   | 58   |                |      |                | +       |        |
|  |  | f   | 58   |                |      |                | +       |        |
|  |  | f   | 62   |                |      |                | +       |        |
| Murphy <sup>35</sup> *                     | 18                                     |     |      | 578            |      |                | +       |        |
| Neusser <sup>85</sup> †                    | 1                                      |     | 44   |                |      | +              |         |        |
| Schroll <sup>57</sup>                      | 1                                      | m   | 26   |                |      |                | +       | +      |
| Schur <sup>88</sup>                        | 1                                      |     |      |                |      |                |         | +      |
| Schwanke <sup>8</sup>                      | 1                                      | f   | 54   | 192            | 52   |                | +       |        |
| Stenstam <sup>31</sup>                     | 8                                      | m   | 44   |                |      | +              |         |        |
|  |  | f   | 33   |                |      |                |         | +      |
|  |  | f   | 35   |                |      | +              |         |        |
|  |  | f   | 43   |                |      |                | +       |        |
|  |  | f   | 46   |                |      | +              |         |        |
|  |  | f   | 58   |                |      |                | +       |        |
|  |  | f   | 58   |                |      |                | +       |        |
|  |  | f   | 72   |                |      |                | +       |        |
| Troll <sup>89</sup>                        | 1                                      |     |      |                |      |                | +       |        |
| Vedder <sup>76</sup>                       | 1                                      | m   |      |                |      |                | +       |        |
| Weese <sup>90</sup>                        | 1                                      | f   | 61   | 370            |      |                | +       |        |
| Wilkinson <sup>34</sup>                    | 3                                      |     |      |                |      | +              |         |        |
|  | 75                                     |     | 2603 | 1621           |      |                |         |        |

\* Murphy states only that exophthalmic goiter was the first disease in eight cases  
† Same case was published by Chvostec and by Decastello

TABLE III  
Incidence of the Combination of Pernicious Anemia and Hyperthyroidism

|                                   | Total no admissions to hospital | No cases pernicious anemia | No cases Graves' disease | No cases Graves' disease and pernicious anemia |
|-----------------------------------|---------------------------------|----------------------------|--------------------------|--|
| Andrus and Wintrobe <sup>32</sup> | 30,208                          | 335                        | 626                      | 2  |
|                                   | 19,535                          | 95                         | 504                      | 3  |
| Stenstam <sup>31</sup>            | 28,411                          | 192                        | 389                      | 3  |
| Totals                            | 78,154                          | 622                        | 1519                     | 8  |

Analysis of table 2 indicates that the incidence of hyperthyroidism in pernicious anemia is only 0.6 per cent, whereas the incidence of pernicious anemia in hyperthyroidism is 1.9 per cent. Stenstam <sup>31</sup> and Andrus and Wintrobe <sup>32</sup> surveyed the number of cases of pernicious anemia and hyperthyroidism occurring separately and in combination, and compared these with the total hospital admissions (table 3). From their data we can calculate the correlation factor to be 0.005, i.e., mathematically a real relationship is improbable.

We present here in detail an interesting coincidence of hyperthyroidism and pernicious anemia in an elderly female whom we have had the opportunity of observing closely over 20 months of continuous hospitalization.

#### CASE REPORT

C. C., a 65 year old white female, was first admitted to the Metropolitan Hospital on October 21, 1942 complaining of extreme weakness, dyspnea, palpitation, headache, tinnitus, and blurred vision. These symptoms, which had their onset shortly after the death of her husband five years previously, were markedly aggravated in the few weeks prior to admission, and were occasionally associated with vomiting. Of note in the past history were two operations: the first one a bilateral ovariectomy at the age of 26, the reason for which is unknown, and the second a subtotal thyroidectomy at the age of 58 for hyperthyroidism.

Physical examination revealed a chronically ill, thin, pale elderly white female who was confused and disoriented. The mucous membranes were pale, the tongue was smooth, pink, and uncoated. In the region of the thyroid gland there was a well-healed collar incision underneath which a small amount of thyroid tissue was palpable. The cardiac sounds were regular and of good quality, with a moderate accentuation of the second aortic sound, a loud blowing systolic murmur was audible over the whole precordium. The lungs were clear. The liver and spleen were not palpable. The deep tendon reflexes were hypoactive, but no pathological reflexes were elicited.

A blood count showed 40 per cent hemoglobin, with 1.6 million erythrocytes and 3,650 leukocytes per cu mm, and a differential white count of which polymorphonuclears comprised 45 per cent, lymphocytes 48 per cent, and monocytes 8 per cent. The sternal marrow was diffusely megaloblastic. The icteric index was 8.5, and the van den Bergh reaction was of the direct, delayed type. On gastric analysis, no free hydrochloric acid was found.

The patient responded well to the administration of liver extract and small transfusions. Her sensorium cleared, strength returned, and the symptomatology present on entry disappeared. She was discharged to the Out-Patient Department on November 19, 1942, where her pernicious anemia was satisfactorily treated until February 6, 1943. On the latter date she was returned to the hospital complaining of marked

nervousness, dizziness, tingling in the extremities, weakness, dyspnea, palpitation, and insomnia

Physical examination then revealed a hyperkinetic, apprehensive elderly woman, well oriented for time and place. Marked exophthalmos was present, with moderate lid-lag and difficulty in convergence. There was a gross tremor of the hands, but the deep tendon reflexes were hypoactive. Hypesthesia was present in both feet, and the vibratory sense was diminished over the lower leg. The remainder of the examination was not remarkable.

Her basal metabolic rate, which had been plus 70 per cent in the clinic several days before admission, was now plus 34 per cent. The findings on examination of the blood were hemoglobin 80 per cent, and 5.93 million erythrocytes and 5,600 leukocytes per cu mm, with a differential white cell count of 50 per cent polymorphonuclears, 46 per cent lymphocytes, and 4 per cent monocytes. The blood sugar, urea nitrogen, and creatinine levels were within normal limits. Gastric analysis again yielded no free hydrochloric acid, even after injection of histamine. Roentgenograms of the skull demonstrated a normal sella turcica and normal clinoid processes. In the electrocardiogram, many auricular and ventricular extrasystoles were noted. The circulation time, performed by the fluorescein method of Lange,<sup>36, 37</sup> was 15 seconds from arm to lip, and 31 seconds from arm to leg.

Injection of liver extract at this time was immediately followed by a sensitivity reaction characterized by marked itching and flushing, both immediately relieved by the intravenous administration of calcium gluconate. As the blood picture subsequently remained within normal limits, no further injection of liver was attempted.

Because the patient was opposed to operation and because we thought that her hyperthyroidism might be secondary to pituitary overactivity, she was given desiccated thyroid, gr 1/10 daily. Some clinical improvement was noted, despite the fact that the basal metabolic rate on February 25 was plus 53 per cent. Subsequent determinations, made at approximately monthly intervals, ranged between plus 28 per cent and plus 63 per cent.

Early in April, of 1943, the patient showed signs of mental confusion, later becoming irrational, disoriented, and finally stuporous. About this time, too, auricular fibrillation developed, which persisted for more than one year. Examination of the peripheral blood and of the bone marrow revealed no abnormalities. The patient was given 50 mg each of thiamin chloride, nicotinamide, and cevitamic acid intravenously daily for four days, with a complete return to consciousness and clearing of the sensorium. Adequate vitamin supplements were thereafter continued by mouth.

During the succeeding six months, the patient's status changed little, there was no weight loss and few subjective complaints, in spite of a persistently elevated basal metabolic rate. During November and December, 1943, the clinical signs of hyperthyroidism increased, weight loss, irritability, marked perspiration, and tremor. Therefore, in January, 1944, thiouracil 0.4 gm daily, was prescribed, following which a complete remission of all symptoms and signs of hyperthyroidism occurred. The basal metabolic rate fell to plus 4 per cent, and the auricular fibrillation was replaced by a normal sinus rhythm. The details of the patient's course during thiouracil therapy are more fully reported elsewhere.<sup>38</sup>

## DISCUSSION

The sequence of events in the above case is rather interesting. It is clear that the hyperthyroidism was present a considerable period of time before the pernicious anemia occurred. Following sub-total thyroidectomy, the metabolic status remained normal for seven years, during which pernicious anemia made its appearance. The second episode of hyperthyroidism developed while the

pernicious anemia was regressing under treatment with injections of liver extract. It is noteworthy that the pernicious anemia continued into full remission in the face of a full-blown hyperthyroidism, which of itself might have been expected to produce a pseudo-pernicious anemia picture. It is of no great moment that the patient did not require more liver injections to maintain a normal blood picture after they were discontinued in February, 1943, as a result of sensitivity. It is well known that patients with pernicious anemia remain clinically well after a few initial doses of liver, in fact, spontaneous remissions are not uncommon.

That the nutritional needs of the body may be greatly increased by hyperthyroidism is forcefully illustrated by the stuporous state our patient developed in April, 1944. The condition simulated that of an advanced arteriosclerotic cerebral degeneration and was only completely differentiated from it when it was dramatically relieved by parenteral vitamin therapy. Although the increased needs for vitamins A and B<sub>1</sub> in hyperthyroidism have been well established, little attention has been devoted to a study of nicotinic acid, the use of which had such a striking effect in our patient.

The simultaneous occurrence of hyperthyroidism and pernicious anemia naturally raises the question of the influence of each disease upon the other.

*Some Physiologico-Pathologic Considerations of Thyreo-Hematopoietic Relationships* Since many authors have discussed the influence of the thyroid gland on blood formation, it is surprising that the bone marrow has not been examined more frequently in uncomplicated hyperthyroidism. Only 10 cases are reported wherein such examinations were performed. In two of these cases,<sup>39</sup> only the ribs were examined, and these were found to be normal. Of the others, seven showed red bone marrow<sup>40, 41, 42, 43, 44</sup>. In Rautmann's case<sup>42</sup> the extremely large number of eosinophilic myelocytes was striking, as was the moderate number of erythroblasts. There were no findings in vivo to explain the presence of red bone marrow. One of Pettavel's patients, who also had red bone marrow, exhibited a normal blood picture while alive.<sup>39</sup> Wegelin<sup>45</sup> described yellow marrow in one case. Despite the hyperplasia of the marrow noted in more than half these cases, a direct effect of the thyroid on the bone marrow was not established.

Nor is the influence of the thyroid on blood formation clearly illustrated by cases of hyperthyroidism combined with pernicious anemia. Red marrow was noted in two such cases by Meulengracht<sup>30</sup> and in one case by Lichtenstein.<sup>46</sup> The latter also found atrophy of the pituitary and thyroid glands. Zondek<sup>16</sup> advocated the administration of thyroid powder in cases of anemia. It was asserted that some patients with pernicious anemia do not improve on liver therapy alone, but only after the addition of thyroid. Wilkinson,<sup>34</sup> however, felt there was "little evidence in favor" of the theory that thyroid substance was necessary for hemopoiesis.

On the other hand, a definite stimulation of the bone marrow by thyroid is claimed by some investigators in animal experiments. Parhon and Parhon<sup>47</sup> noted red bone marrow, cell proliferation, vasodilatation, and *les vesicules adipceuses*. Lida,<sup>48</sup> working with rabbits, considered the spleen necessary for proper stimulation of the marrow. Mansfield<sup>50</sup> claimed the existence of a second thyroid hormone the action of which is primarily upon the bone marrow.

Kunde, Green, and Burns<sup>51</sup> studied the influence of thyroid feeding on rab-

nts, and noted an initial polycythemia and increase in hemoglobin. The bone marrow was "less fatty than normal." Besides the polycythemia, they also observed many eosinophiles and myelocytes. Lim and Brown<sup>52</sup> noted bone marrow stimulation only in young rabbits.

The observations of Marine<sup>53</sup> are of great importance. He produced hyperplasia of the thyroid in fishes and in rats by feeding them liver one to three days old. Animals receiving either fresh liver or liver four to six days old maintained normal or nearly normal thyroid glands. Marine concluded that "the diet is only a contributing factor, and it may act by increasing the work of the thyroid in order to maintain a general increase in metabolism, especially in connection with the overfeeding of nutritionally incomplete diets."

In some cases of pernicious anemia, the thyroid gland was examined post mortem. It was found enlarged once in 30 cases reported by Neumann<sup>54</sup>. In 13 cases reported by Mendershausen,<sup>55</sup> only one had a normal thyroid, in the remainder, the gland was atrophic and infiltrated with lymphocytes, and new colloid was sometimes present. Kerppola<sup>57</sup> noted enlargement of the thyroid gland in five of 107 patients with pernicious anemia. Schaumann and Saltzmann<sup>56</sup> made similar observations.

In two cases of pernicious anemia, Holler<sup>56</sup> found no iodine in the thyroid. This is of interest because of his claim<sup>57</sup> to have found a hemolysin in the blood of hyperthyroid patients "which (is) similar to that in cases of pernicious anemia and acts as a hemo- and myelotoxic agent." Pappenheim has propounded a similar theory.<sup>58</sup>

Employing the hippuric acid test, Bartels and Perkin<sup>59</sup> found that hepatic damage in exophthalmic goiter was more frequent and more severe than had previously been suspected. Similar results were reported by Haines, Magath, and Power<sup>60</sup>. Rowe<sup>61</sup> found hepatic dysfunction in 22.4 per cent of 664 cases, far more than in any other endocrinopathy. Pende,<sup>62</sup> too, noted hepatic damage in Graves' disease, he also found the same abnormalities of the leukocytes in hyperthyroidism as in pernicious anemia.

Pathological examinations of the liver in Graves' disease are quite striking. Haban<sup>63</sup> speaks of "cirrhosis Basedowni." Cameron and Karunaratne<sup>64</sup> observed changes in hepatic structure in 20 of 30 cases. Weller<sup>65</sup> studied a group of 48 cases in which all possible causative factors of hepatitis were eliminated. Sixteen showed slight chronic hepatitis, and 26 exhibited marked involvement, the structural changes varied from chronic hepatitis to necrotizing processes. Beaver and Pemberton<sup>66</sup> reported similar findings.

*Age and Sex Incidence of Hyperthyroidism and Pernicious Anemia* There is a difference in the age incidence of pernicious anemia and Graves' disease. Patients with hyperthyroidism are under 20 or between 20 and 40 years old, according to Goldzieher<sup>67</sup> and Deusch,<sup>68</sup> whereas those with pernicious anemia are usually between the ages of 40 and 60.<sup>69</sup> Murphy<sup>35</sup> found the average age of patients with pernicious anemia to be 55 years. In 72 per cent of his cases, the disease was discovered after the fiftieth year.

Exact statements about age and sex are available in 37 patients reported to have both pernicious anemia and hyperthyroidism. Thirty were female, five male, and two were not specifically designated. A majority of the patients were between 30 and 50 years old (table 4), with the males averaging 32.4 years, and



TABLE IV

Age Distribution in Patients Suffering from Pernicious Anemia and Hyperthyroidism

| Age    | Sex |    |   | Total |
|--------|-----|----|---|-------|
|        | M   | F  | ? |       |
| 15     | 1   |    |   | 1     |
| 20-29  | 2   | 1  |   | 3     |
| 30-39  |     | 11 | 1 | 12    |
| 40-49  | 1   | 7  | 1 | 9     |
| 50-59  | 1   | 7  |   | 8     |
| 60-69  |     | 3  |   | 3     |
| 72     |     | 1  |   | 1     |
| Totals | 5   | 30 | 2 | 37    |

the females 45.1 years. Sixteen of the 37 patients were younger than 40 years. It is apparent, then, that pernicious anemia becomes manifest earlier than usual if it is combined with hyperthyroidism.

*The Reciprocal Influence of Hyperthyroidism and Pernicious Anemia upon Each Other* Of the 75 patients whose histories are summarized (table 2), statements are available on the first disease diagnosed in only 56 cases. Forty-two (75.0 per cent) showed evidence of hyperthyroidism prior to the onset of pernicious anemia, 10 (17.9 per cent) presented the reverse sequence of events, and four (7.1 per cent) apparently developed both diseases simultaneously.

When hyperthyroidism was the first disease diagnosed, pernicious anemia made its appearance any time between one and 30 years later, the average being 15.5 years. When pernicious anemia was the initial disease, hyperthyroidism supervened from one-half to nine years later, with an average of four years.

It has been stated by various authors that the course of either hyperthyroidism or pernicious anemia is not changed by the superimposition of the other. Giffin and Bowler,<sup>33</sup> for example, say "There was nothing to indicate . . . a modification of the course of either disease." Others, however, like Meulengracht,<sup>30</sup> assert that the symptoms of Graves' disease more or less disappeared after the development of pernicious anemia.

In the published case histories, data are available in 49 instances on the thyroid manifestations present when pernicious anemia was diagnosed, these are detailed in table 5. A critical analysis of the figures in this table reveals

TABLE V

Thyroid Manifestations Present When the Diagnosis of Pernicious Anemia Was Made (49 cases)

|   | No. times observed | Per cent |
|---|--------------------|----------|
| Exophthalmos only                           | 7                  | 14.3     |
| Increased basal metabolic rate              | 14                 | 28.6     |
| Remaining manifestations of Graves' disease | 7                  | 14.3     |
| All symptoms of Graves' disease             | 7                  | 14.3     |
| No symptoms of Graves' disease              | 11                 | 22.4     |
| Hypothyroidism had developed <sup>1</sup>   | 3                  | 6.1      |
| Total                                       | 49                 | 100.0    |

<sup>1</sup> In one case of Kerppola<sup>27</sup> it is not certain whether or not a hypofunction of the thyroid had developed.

that the number of cases in which Graves' disease existed when the second disease was diagnosed is actually smaller than appears at first glance. For example, it is known that exophthalmos is one of the most difficult manifestations to influence, and that it frequently persists after the hyperthyroidism is completely cured clinically. Thus it may be assumed that the seven patients having only exophthalmos, had no real evidence of hyperthyroidism.

Similar caution must be exercised in interpreting basal metabolic rates. Elevated percentages are listed in 14 instances, the figures given by Murphy<sup>35</sup> are excluded, since he merely stated that the values ranged between plus 20 per cent and plus 62 per cent. In the tabulated cases, the basal metabolic rate varied between plus 15 per cent and plus 114 per cent, with an average of 42.3 per cent. Since Becker<sup>70</sup> pointed out that the basal metabolism in pernicious anemia alone may be increased to as high as plus 28 per cent, we cannot diagnose hyperthyroidism when pernicious anemia is also present if the rate is below plus 30 per cent. On this basis, five of the 14 tabulated cases must be excluded. Furthermore, we may presume that three of the 49 patients had developed a hypofunction, and in seven it is questionable whether signs of hyperfunction still existed. Thus, the diagnosis of hyperthyroidism is doubtful in almost half the cases, and the ameliorating effect of the supervening pernicious anemia is questionable.

Of further interest is the fact that Meulengracht,<sup>30</sup> Murphy,<sup>35</sup> and others expressly state that their patients never developed features of myxedema if pernicious anemia were present with the hyperthyroidism. An obvious hypofunction existed in only three, perhaps four, cases. In one of Murphy's cases the basal metabolic rate dropped to minus 26 per cent, and in one of Adler's<sup>71</sup> from plus 67 per cent to minus 27 per cent. In the case observed by Gulland and Goodall,<sup>72</sup> "the symptoms (of Graves' disease) had given place to those of myxedema" shortly *before* pernicious anemia developed. Similar doubts exist concerning the direct influence of pernicious anemia in Kerppola's patient.<sup>27</sup>

On the other hand, there is less question about the influence exerted by the development of hyperthyroidism in cases of preëxistent pernicious anemia. It is recognized that the symptoms of this blood disease may be replaced by an entirely new symptom complex, such transformations were emphasized by Naegeli<sup>69</sup> in one case of tuberculosis and in one of heart failure, and by Weinberg<sup>73</sup> in a patient who developed cancer of the stomach. The most characteristic feature in patients with pernicious anemia after the development of Graves' disease is the loss of weight. Pathological pigmentation has also been observed.<sup>30</sup> However, each of these alterations can be attributed to Graves' disease alone, without necessarily implying that the antecedent pernicious anemia played a part.

*Etiological Factors in Hyperthyroidism and Pernicious Anemia* Theories on the pathogenesis of each of the two diseases individually are manifold, but only those will be mentioned which perhaps indicate the relationship of the one to the other. For example, one group of authors considered a constitutional basis, e.g., Meulengracht, whereas others, like Stenstam,<sup>31</sup> denied its importance. The physical features of patients with pernicious anemia are quite different from those with Graves' disease. The latter are young, slender, and lose weight easily. The former are older, rather stout, and exhibit no tendency to weight loss.

Furthermore, if the two diseases were genetically related, one should expect them to occur frequently in a given family. As far as we could determine, there

have been only three histories published in which both diseases occurred in the same family. Reference has already been made to one, mentioned by Murphy<sup>85</sup>. Another, reported by Hirsch,<sup>74</sup> concerned a patient with pernicious anemia, one sister died of pernicious anemia, while another suffered from Graves' disease. The third instance, reported by Benjamin,<sup>75</sup> was that of a patient with pernicious anemia and diabetes mellitus whose mother had an extremely severe thyrotoxicosis. One of us (F B) had occasion to treat a patient with hyperthyroidism whose mother, grandfather, and two paternal uncles died of pernicious anemia.

Vedder<sup>76</sup> considered Graves' disease to be a deficiency state; moreover, he attributed the pathogenesis of pernicious anemia to a diet poor in protein. In stressing the similarity of the two processes, he emphasizes diarrhea, achylia, and increased basal metabolic rate as common to both. Pappenheim<sup>58</sup> noted the occurrence of pernicious anemia following shock or toxicosis, an etiology quite common in thyrotoxicosis. Pende<sup>62</sup> emphasized the similarity of the white blood cell picture in the two diseases.

The etiologic rôle of achlorhydria in the anemias of hyperthyroidism is not convincing, even though achylia does occur in cases of long-standing Graves' disease. Hansen,<sup>77</sup> Meulengracht,<sup>30</sup> and Fleischhans<sup>14</sup> suggest, rather, that it may be *one* factor which makes pernicious anemia manifest (without actually being a direct cause). A contributory rôle may also be played by the hepatic damage found in Graves' disease, especially when combined with achlorhydria.

The question has been raised whether the second disease, be it pernicious anemia or hyperthyroidism, is caused by the therapy used for the first. Some authors have felt that the treatment of pernicious anemia by liver may be responsible for subsequent hyperthyroidism, but the evidence at best is tenuous. In a few instances where pernicious anemia followed hyperthyroidism, radiation of the thyroid may have been responsible, perhaps by producing myxedema and its attendant pernicious anemia-like picture. Hansen,<sup>77</sup> for example, observed the development of pernicious anemia "acutely, directly after a course of roentgen treatment. The causal connection seemed unquestionable, although pre-existing achylia may have afforded a predisposition." Similar instances have been noted after thyroidectomy, but in none of them can other factors be excluded.

If all factors are critically analyzed, it becomes apparent that the co-existence of hyperthyroidism and pernicious anemia is only fortuitous, and that no demonstrable causal relationship exists.

#### SUMMARY AND CONCLUSIONS

Seventy-six cases, including that herein reported, of co-existent hyperthyroidism and pernicious anemia have been published in the literature; of these, 50 were described by six authors.

Three-fourths of all these patients exhibited evidence of hyperthyroidism before the onset of symptoms of pernicious anemia. Ten presented the reverse sequence. Four apparently developed both diseases simultaneously.

A secondary hypofunction of the thyroid developed in only three cases following the onset of pernicious anemia, and hyperfunction disappeared in a number of others.

Roentgen therapy of the thyroid in Graves' disease may be of causal significance for the development of pernicious anemia in a very few cases, but the theories of association advanced by various authors are not convincing. Some

stress the achlorhydria, others the liver damage, and still others the constitutional factor

The long interval between the development of the two diseases, and the extremely low correlation factor afford no support for a cause-effect relationship between them. Further studies of the influence of the thyroid gland on blood formation are necessary before definite conclusions can be reached

## BIBLIOGRAPHY

- 1 KOCHER, A. Morbus Basedowii, In: *Spez Path u Ther d inn Krankh* (Kraus and Brugsch), 1919, Urban & Schwarzenberg, Berlin and Wien, 1, 751
- 2 PLUMMER, W. A. The blood picture in exophthalmic goiter, *Minnesota Med*, 1919, 11, 330
- 3 JACKSON, A. S. The blood picture in 600 cases of goiter, *Jr Am Med Assoc*, 1931, xcvi, 1954
- 4 McCULLAGH, E. P., and DUNLAP, J. H. The blood picture in hyperthyroidism and in hypothyroidism, *Jr Lab and Clin Med*, 1931-1932, xvii, 1060
- 5 WAHLBERG, J. Das Thyrotoxicosesyndrom und seine Reaktion bei kleinen Joddosen, *Acta med Scandinav*, 1926, Suppl xiv, 3
- 6 DEUSCH. Schilddrüse und Hämatopoese, *Zentralbl f inn Med*, 1927, xlviii, 952
- 7 ZIMMERMANN, O. Zur Klinik des M. Basedow unter besonderer Berücksichtigung des Blutbildes, *Wien klin Wchnschr*, 1933, xli, 265
- 8 SCHWANKE, W. Basedow'sche Krankheit und rotes Blutbild, *Klin Wchnschr*, 1936, xv, 346
- 9 BLANK, G. Blutbefunde bei Hyperthyreose und Struma, *Deutsch Arch f klin Med*, 1920, cxxii, 16
- 10 JOLL, C. A. Diseases of the thyroid gland, 1942, W. Heinemann, London
- 11 MEANS, J. H. The thyroid and its diseases, 1937, L. B. Lippincott Co., Philadelphia
- 12 LAWRENCE, C. H., and ROWE, A. W. Studies of the endocrine glands. III. The thyroid, *Endocrinology*, 1928, xii, 377
- 13 CROTTI, A. Diseases of the thyroid, parathyroid and thymus, 3d ed., 1938, Lea & Febiger, Philadelphia
- 14 FLEISCHMANN, B. [Case of pernicious anemia associated with Graves' disease], *Časop lék česk*, 1934, lxxiii, 1456. Abstr. in *Sang*, 1935, ix, 642
- 15 KLEINER, G., and RENYI-VAMOS, F. Die Änderungen der Erythrocytenzahl während des Verlaufes der Hyperthyreose, *Deutsch med Wchnschr*, 1938, lxiv, 1144
- 16 ZONDEK, H. Der Einfluss kleiner Thyreoidinmengen auf das rote Blutbild, *Deutsch med Wchnschr*, 1923, xlviii, 1033
- 17 BLISS, T. L. Basal metabolism in polycythemia vera, *Ann Int Med*, 1929, 11, 1155
- 18 DITTMAR, F. Zwischenhirnschädigung und Polyzythämie nach Kohlenoxydintoxikation, *Deutsch med Wchnschr*, 1939, lvi, 500
- 19 HUMPHRY, L. The parathyroid glands in Graves' disease, *Lancet*, 1905, 11, 1390
- 20 PENDE. Quoted by NATHAN, M. Erythremies protopathiques et diencephale, *Presse med*, 1931, xxxix, 403
- 21 SÄTTLER, H. Die Basedow'sche Krankheit, 1909, W. Engelmann, Leipzig
- 22 TYRRELL, E. J. Polycythemia vera (rubra) complicated with hyperthyroidism, *Brit Med Jr*, 1919, 11, 596
- 23 ZONDEK, H. Die Krankheiten der endokrinen Drüsen, 2d ed., 1926, J. Springer, Berlin
- 24 MEANS, J. H., LERMAN, J., and CASTLE, W. B. Coexistence of myxedema and pernicious anemia, *Trans Assoc. Am Phys*, 1930, xlv, 363
- 25 YOUNG, J. B. Quoted by BURWELL, C. S., SMITH, W. C., and NEIGHBORS, DEW. The output of the heart in thyrotoxicosis, with the report of a case of thyrotoxicosis combined with primary pernicious anemia, *Am Jr Med Sci*, 1929, clxxviii, 157

- 26 SCHAUMANN, O, and SALTZMANN, F Die perniziose Anämie, In *Håndbuch der Krankheiten des Blutes (Enzyklopadie d klin Med, Spez Teil)* 1925, J Springer, Berlin, 11, 100
- 27 KERPPOLA, W Står den pernicioosa anemien i något förhållande till skoldkörtelfunktionen? *Finska Lakares Handl*, 1923, lxxv, 330
- 28 SUZMAN, M M The basal metabolism in pernicious anemia and subacute combined degeneration of the spinal cord, *Am Jr Med Sci*, 1932, clxxxiv, 682
- 29 DAVIDSON, L S P, and GULLAND, G L Pernicious anaemia, 1930, H Kimpton, London.
- 30 MEULENGRACHT, E Morbus Basedowii und perniziose Anämie, *Klin Wchnschr.*, 1929, viii, 18
- 31 STENSTAM, T Pernicious anemia and Basedow's disease, *Acta med Scandinav*, 1940, civ, 29
- 32 ANDRUS, E C, and WINTROBE, M M A note upon the association of hyperthyroidism and pernicious anaemia, *Bull Johns Hopkins Hosp*, 1936, lxx, 291
- 33 GIFFIN, H Z, and BOWLER, J P Diseases which may be associated with pernicious anemia, *Minnesota Med*, 1923, vi, 13
- 34 WILKINSON, J F Diseases associated with pernicious anaemia, *Quart Jr Med*, 1933, 11, 281
- 35 MURPHY, W P Anemia in practice, 1939, W B Saunders, Philadelphia
- 36 LANGE, K, and BOYD, L J The technique of the fluorescein test to determine the adequacy of circulation in peripheral vascular diseases, the circulation time and capillary permeability, *Bull New York Med College, Flower & Fifth Ave Hosps*, 1943, vi, 78
- 37 LANGE, K, and KREWER, S E The dermofluoremeter, *Jr Lab and Clin Med*, 1943, xxviii, 1746
- 38 MCGAVACK, T H, GERL, A J, VOGEL, M, and SCHWIMMER, D The treatment of 26 thyrotoxic patients with thiouracil and a review of toxic reactions in all (135) reported cases, *Jr Clin Endocrinol*, 1944, iv, 249
- 39 PETTAVEL, C A Beitrag zur pathologischen Anatomie des Morbus Basedowii, *Deutsch. Ztschr f Chir*, 1912, cxvi, 488
- 40 GRAUPNER Nierenerkrankungen bei Basedow'scher Krankheit, *Munch med Wchnschr*, 1910, lvii, 1695
- 41 v HABERER Quoted by WEGELIN <sup>45</sup>
- 42 RAUTMANN, H Pathologisch-anatomische Untersuchungen über die Basedow'sche Krankheit, *Mitt a d Grenzgeb d Med u Chir*, 1915, xxviii, 489.
- 43 MATTI, H Ueber die Kombination von Morbus Basedowii mit Thymushyperplasie, *Deutsch Ztschr f Chir*, 1912, cxvi, 425
- 44 SCHNITZLER, J [Morbus Basedowii], (*Soc proc*), *Wien klin Wchnschr*, 1894, vii, 371.
- 45 WEGELIN, C SCHILDDRUSE, In *Handb d spez path Anat u Histol* (Henke and Lubarsch), 1926, J Springer, Berlin, viii, 1
- 46 LICHTENSTEIN, K Ueber die Disposition zu perniziose Anämie, *Krankheitsforschung*, 1928, vi, 195
- 47 PARHON, C, and PARHON, C Note sur la reaction de la moelle osseuse dans l'hyperthyroïde expérimentale, *Compt-rend Soc de biol*, 1911, lxxi, 329
- 48 LIDA, Y Influence of thyroid gland on recovery of anemia due to loss of blood, *Trans Soc Path Jap*, 1936, xxvi, 477
- 49 MANSFELD, G, and SOS, J Schilddruse und perniziose Anämie, *Klin Wchnschr*, 1938, xvii, 386
- 50 MANSFELD, G La glande thyroïde et l'anémie pernicieuse, *Presse méd*, 1938, xlii, 993
- 51 KUNDF, M M, GREEN, M F, and BURNS, G Blood changes in experimental hypo- and hyperthyroidism, *Am Jr Physiol*, 1932, xcix, 469
- 52 LIM, R K S, SARKAS, B B, and BROWN, J P H G The effect of thyroid feeding on the bone marrow of rabbits, *Jr Path and Bact*, 1922, lxxv, 228

- 53 MARINE, D Observations on the etiology of goitre in brook trout. *iv Jr Exper Med*, 1915, *xxi*, 452
- 54 NEUMANN, W J Ueber progressive perniciose Anämie, Diss, Leipzig, 1901
- 55 MENDERSHAUSEN, A. Histologische Untersuchung der endokrinen Organe bei perniziöser Anämie, *Klin Wchnschr*, 1925, *iv*, 2105
- 56 HOLLER, G Kurze Mitteilung von Versuchsergebnissen über die Verteilung und Wirkungsweise parenteral eingeführten Jods im gesunden und kranken menschlichen Organismus, *Klin Wchnschr*, 1923, *ii*, 1692
- 57 HOLLER, G Zur Klinik der Beeinflussung der Haematopoese durch die Schilddrüse, *Wien klin Wchnschr*, 1923, *xxxvi*, 23
- HOLLER, G System der Anämien, *Ztschr f klin Med*, 1926, *ciii*, 1
- 58 PAPPENHEIM, A Unsere derzeitigen Vorstellungen vom Wesen, Ursachen und Zustandekommen der perniciosen Anämie, *Folia haematol*, 1918-1919, *xxiii*, I Teil, 149
- 59 BARTELS, E C, and PERKIN, H J Liver function in hyperthyroidism as determined by the hippuric acid test, *New England Jr Med*, 1937, *ccxvi*, 1051
- 60 HAINES, S F, MAGATH, T B, and POWER, M H The hippuric acid test in hyperthyroidism, *Trans Am Assoc. Study Goiter*, 1939, 277
- 61 ROWE, A W Endocrine studies *xxv* The association of hepatic dysfunction with thyroid failure, *Endocrinology*, 1933, *xvii*, 1
- 62 PENDE, N *Endocrinologia*, 4th ed, 1934, Vallardi, Milano
- 63 HABAN Quoted by BARTELS and PERKIN <sup>59</sup>
- 64 CAMERON, G R, and KARUNARATNE, W A E Liver changes in exophthalmic goitre, *Jr Path and Bact*, 1935, *xli*, 267
- 65 WELLER, C V Hepatic pathology in exophthalmic goiter, *Ann Int Med*, 1933, *vii*, 543
- 66 BLAVER, D C, and PEMBERTON, J DE J The pathologic anatomy of the liver in exophthalmic goiter, *Ann Int. Med*, 1933, *vii*, 687
- 67 GOLDZIEHER, M A The endocrine glands, 1939, D Appleton-Century Co, New York.
- 68 DEUSCH, G Die Hyperthyreosen, In *Handb d inn Sekretion* (Hirsch), 1928, C Kabitsch, Leipzig, *iii*, Hft. 1
- 69 NÄGELI, O *Blutkrankheiten und Blutdiagnostik*, 4th ed, 1923, J Springer, Berlin
- 70 BECKER, G Studien über den Stoffwechsel bei perniziöser Anämie, *Acta med Scandinav*, 1926, *lxxiii*, 478
- 71 ADLER, E Fall av Morbus Basedowii och anaemia perniciosa, *Nord med tidskr*, 1936, *xi*, 524
- 72 GULLAND, G L, and GOODALL, A The blood, 3d ed, 1925, W Green & Son, Edinburgh
- 73 WEINBERG, F Karzinom und perniziose Anämie, *Ztschr f klin Med*, 1918, *lxxxv*, 392
- 74 HIRSCH, F Über die Frage der Zunahme der perniciosen Anämie, *Med Klin*, 1927, *xxiii*, 1932
- 75 BENJAMIN, M Die pathogenetischen Beziehungen des Diabetes mellitus zur perniziösen Anämie, *Folia haematol*, 1934, *lii*, 113
- 76 VEDDER, A Zur Pathogenese der perniziösen Anämie, *Ergebn d inn Med u Kinderh*, 1930, *xxxviii*, 272
- 77 HANSEN, I [A case of pernicious anemia complicated with Basedow's disease cured by Roentgen treatment], *Ugesk f Laeger*, 1922, *lxxxiv*, 1643
- 78 AITOFF, W, and LOEWY, G Traitement des anémies graves par la methode de Whipple, *Presse med*, 1927, *xxxv*, 545
- 79 BAUER, J Innere Sekretion, 1927, J Springer, Berlin
- 80 BILLINGS, F A report of cases of pernicious anemia with special reference to the blood-findings, *Am Jr Med Sci*, 1900, *cxx*, 503
- 81 FABER, K Discussion of HANSEN, I Anaemia perniciosa ved Mb Basedowii, *Ugesk. f Laeger*, 1922, *lxxxiv*, 1520
- 82 FERNANDEZ Quoted by REINHOLD, F Morbus Basedowii und Anaemia gravis, *Med. Klin*, 1929, *xxv*, 1097

- 83 HANSSEN, O, and STUB, O Leverdiaet ved anaemi, Tidsskr f d norske Laegefor, 1927, xlvii, 1045
- 84 HEERES Quoted by VEDDER <sup>76</sup>
- 85 LANDSTROM Quoted by SATTLER <sup>21</sup>
- 86 NEUSSER Zur Klinik der perniciosen Anamie, Wien klin Wchnschr, 1899, xii, 388
- 87 SCHROLL, G "Pseudo-sprue," Ugesk f Laeger, 1926, lxxxviii, 276
- 88 SCHUR Quoted by REINHOLD <sup>82</sup>
- 89 TROLL Quoted by STENSTAM <sup>81</sup>
- 90 WEESE, K Perniziose Anamie und Basedow, Klin Wchnschr, 1936, xv, 717

## HEMOLYTIC ANEMIA, HYPERGLOBULINEMIA AND BOECK'S SARCOID \*

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HEMOLYTIC anemia, first described in 1900 by Minkowski<sup>1</sup> and associated with jaundice, increased fragility of the red cells, and spherocytosis, may occur as a congenital disease or may be acquired Dameshek<sup>2</sup> lists chemicals (including sulfa drugs), immune bodies (erythroblastosis fetalis) and various infections and diseases as being responsible for the acquired form Singer and Dameshek<sup>3</sup> reported cases occurring with a dermoid cyst of the ovary, chronic lymphatic leukemia, Hodgkin's, lymphosarcoma, liver disease and pneumonia. Wintrobe<sup>4</sup> refers to reports in the older literature of its occurrence with syphilis, tuberculosis, streptococcal septicemia, paratyphoid fever, cirrhosis of the liver and pregnancy More recent reports mention sarcoma of the spleen, reticulo-endotheliosis, salmonella infection, plumbism, liver disease, and hyperthyroidism in addition to those reported by Singer and Dameshek.<sup>3</sup>

We have encountered a case with recurrence after splenectomy and death in a hemolytic crisis which was associated with Boeck's sarcoid This case is of particular interest and importance in the light of cases reported by Kracke and Hoffman<sup>5</sup> and Jeghers and Selesnick<sup>6</sup> which had a hyperglobulinemia as did our case Haden<sup>7</sup> has also reported one associated with probable sarcoid Our case represents the first instance of hemolytic anemia associated with Boeck's sarcoid proved by autopsy findings

### CASE REPORT

*Present Illness* Mrs H H, a 46 year old white female, was first seen by a physician in September 1944, complaining of pallor, jaundice, weakness, drowsiness and tinnitus in the right ear This followed immediately upon a two week period during which she had three to four drinks each night Fifteen years previously there had been an episode of jaundice, nausea, vomiting and abdominal pain following excessive indulgence in alcohol The episode lasted a few weeks and was regarded as a gall-bladder disturbance With the present illness she was hospitalized and gastrointestinal and gall-bladder roentgenograms were done which were negative During this period she had three transfusions but without significant improvement She remained weak with fainting spells and tachycardia on slight exertion Her

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stools were never gray or white Her hemoglobin is reported to have been 65 per cent She was referred to physicians in New York where, after blood studies showing anemia, spherocytosis, reticulocytosis and increased red cell fragility, a diagnosis of hemolytic anemia was made and a splenectomy done on January 2, 1945 Following this the jaundice cleared, the blood findings returned to normal and the clinical symptoms disappeared About two months later (February 28, 1945) she was admitted to this hospital, again complaining of tinnitus, jaundice, and weakness of increasing severity for one week

*Physical Examination* (February 28, 1945) Temperature 101° F, pulse 110, respirations 22, blood pressure 145 mm Hg systolic and 80 mm diastolic The patient was a jaundiced, moderately dyspneic white female about 46 years of age There were no skin rashes and no enlargement of the peripheral lymph nodes The only

TABLE I  
Hematological Chart

|                                  | 12/26   | 1/2     | 1/7     | 1/18    | 2/28   | 3/1      | 3/3   |
|----------------------------------|---------|---------|---------|---------|--------|----------|-------|
| Hemoglobin—%                     | 41      | 60      | 73      | 80      | 23     | 32       | 20    |
| —gm                              |         |         |         |         | 3.9    | 5.4      | 3.5   |
| RBC (millions)                   | 1.81    | 3.34    | 4.1     | 4.56    | 1.36   | 1.43     | 1.58  |
| Nucleated Cell Count (thousands) | 15.6    | 12.3    | 10.2    | 8.3     | 56.0*  | 73.6*    | 66.4* |
| Stern Cells                      |         |         |         |         | 7      |          | 5     |
| Red Series—                      |         |         |         |         |        |          |       |
| Spherocytosis                    | 4+      | 4+      | 0       | 0       | 4+     | 4+       | 4+    |
| Reticulocytes %                  | 44      |         |         | 1       | 12     |          |       |
| Normoblasts                      | Manv    |         |         |         | 33     |          | 37    |
| Erythroblasts                    |         |         |         |         | 14     |          | 12    |
| Megaloblasts                     |         |         |         |         | 4      |          | 4     |
| White Series—                    |         |         |         |         |        |          |       |
| Neutrocytes                      | 47      | 54      | 51      | 66      | 25     |          | 23    |
| Bands                            | 7       | 10      | 9       | 6       | 1      |          | 3     |
| Myelocytes                       | 1       | 0       | 0       | 0       | 0      |          | 0     |
| Lymphocytes                      | 34      | 30      | 30      | 19      | 5      |          | 5     |
| Monocytes                        | 8       | 4       | 8       | 7       | 0      |          | 0     |
| Eosinocytes                      | 2       | 2       | 2       | 1       | 0      |          | 0     |
| Basocytes                        | 1       | 0       | 0       | 1       | 0      |          | 0     |
| Platelets                        | 150,000 | 280,000 | 240,000 | 480,000 | Normal |          |       |
| Red Blood Cell Fragility         | 52-38   |         |         |         | 50-28  |          |       |
| Rh                               |         |         |         |         |        | Positive |       |

\* 50% of the nucleated cells are erythropoietic forms

findings of note were the jaundice, a splenectomy scar in the left upper quadrant of the abdomen and the occurrence of a soft apical systolic murmur

*Laboratory* The hematological findings are indicated in table 1. A bone marrow aspiration done in January showed a marked erythroblastic and normoblastic hyperplasia, 78 per cent of the cells being erythropoietic forms Blood coagulation and prothrombin times were normal The stools were negative for blood, ova and parasites In January the urine showed urobilinogen in dilutions varying from 1 to 10 to 1 to 40 and no bilirubin was present In February the urobilinogen was markedly increased The blood Wassermann reaction was negative The blood cholesterol in January was 280 mg with esters of 195 A galactose tolerance test was normal but the cephalin-flocculation gave a 1+ result The total protein in January was 5.4 with 3.6 per cent albumin and 1.8 per cent globulin, but in March it was 7.6 with an albumin of 3.6 per cent and a globulin of 4.0 The direct Van den Bergh was negative The icteric index was 27 in January and 40 in March

The spleen removed surgically weighed 485 gm Grossly it was dark red and



firm Microscopically it showed marked congestion of the sinusoids and widely separated small follicles. There were no perifollicular hemorrhages or empty sinusoids but the general picture was consistent with the changes found in hemolytic anemia. No foci of necrosis or tubercles were noted.

*Course* During her brief stay in this hospital an attempt was made to improve the patient's condition with repeated small transfusions. There were no transfusion reactions but no significant changes in the blood findings were produced. There was a progressive increase in the temperature to 104° F with increasing weakness and dyspnea and the patient died of anoxemia on the fifth hospital day.

*Autopsy Gross* Only the positive findings are given. On inspection there was moderate jaundice, a healed surgical scar in the left upper quadrant of the abdomen

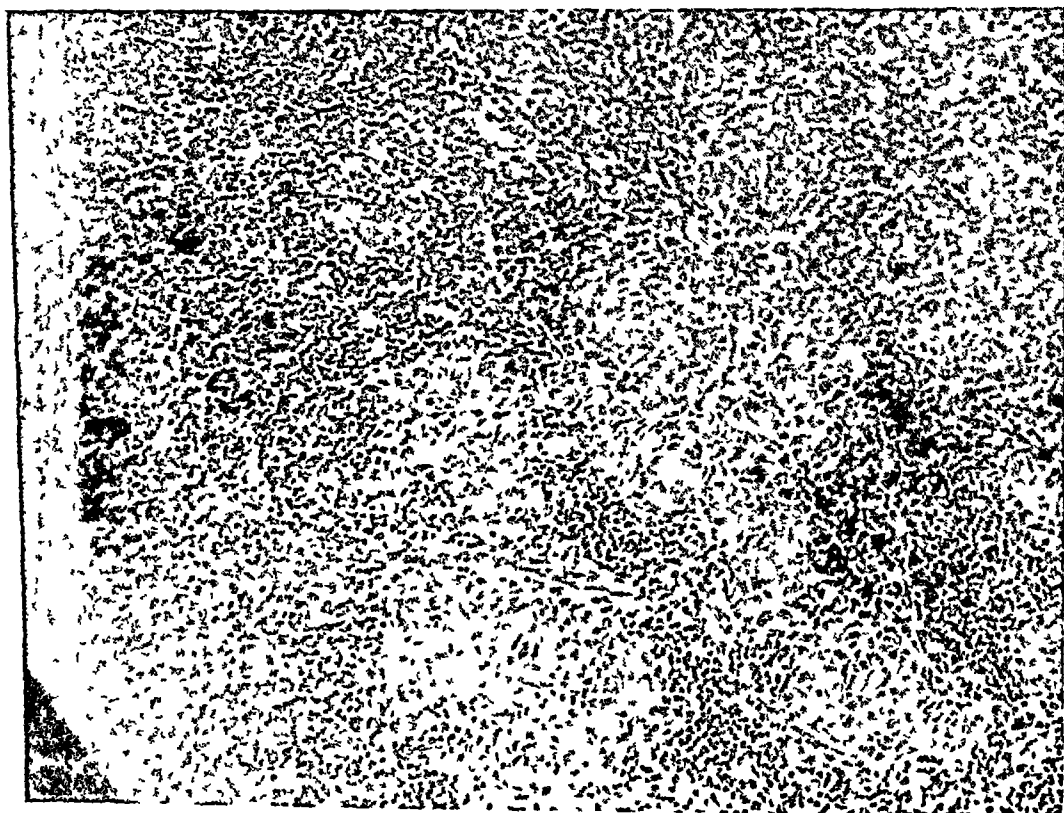


FIG 1 Lymph node showing multiple discrete tubercle-like lesions (sarcoid) composed of giant cells, monocytes and fibroblasts. Phloxine methylene-blue  $\times 100$

and a mild edema of both ankles. The peritoneal, thoracic and pericardial cavities were normal. The heart weighed 360 gm and was normal save for a yellow mottling of the endocardium of the left ventricle. The lungs were normal and there was no evidence of tuberculosis. The spleen was absent, but buried in the periadrenal fat on the left side there were three round red firm nodules measuring 1.2, 0.4, and 0.7 cm in diameter. The pancreas and gastrointestinal tract were normal. The liver weighed 1800 gm, externally it was red-brown and smooth and on section it cut with normal resistance to reveal a firm brown surface with a diffuse pale grayish-yellow mottling. The bile ducts were normal but the gall-bladder contained 50 cc of thick black mucoid material and innumerable small, soft, black calculi measuring up to 0.2 cm in diameter. The right adrenal was normal but the left contained a soft yellow cortical nodule 2.5 cm in diameter. The kidneys, bladder and genital organs were

normal The vertebral, rib and sternal marrows were dark red, jelly-like and soft There was moderate enlargement (three to four times) of the tracheobronchial, para-aortic and pancreatocoeliac lymph nodes, all of which presented soft gray-white slightly granular surfaces The peripheral lymph nodes were not enlarged

*Microscopic* There were foci of erythropoiesis in the lung, kidneys, liver and lymph nodes composed of stem cells, erythroblasts and normoblasts The red nodules in the periadrenal fat were composed of splenic elements containing sinusoids which

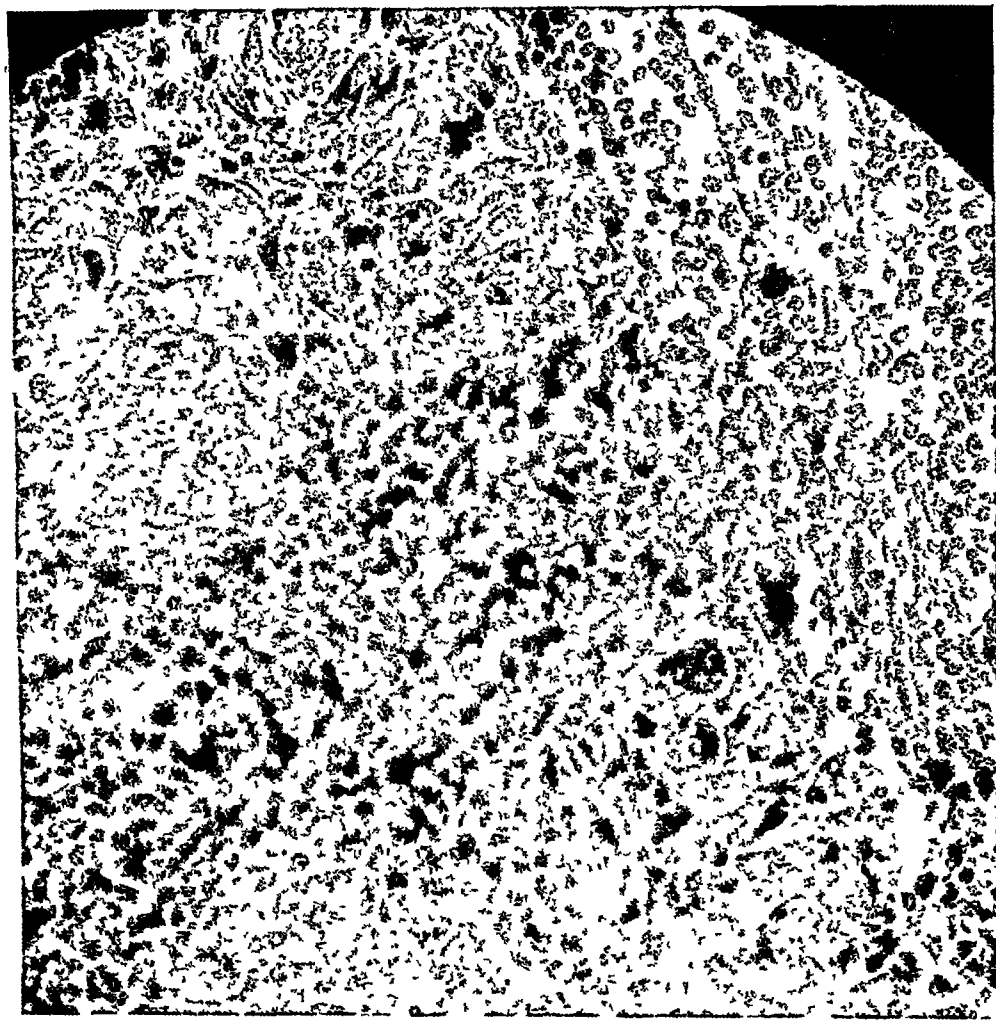


FIG 2 Lymph node showing the detail of the sarcoid lesions under higher magnification  
Phloxine methylene-blue  $\times 400$

were markedly engorged and small lymph follicles with central arterioles of the type encountered in splenic tissue The tracheobronchial, para-aortic and pancreatocoeliac lymph nodes were almost completely replaced by discrete, small tubercle-like lesions composed of a central mass of collagen and lymphocytes and surrounded by swollen eosinophilic monocytes (epithelioid cells), fibroblasts and occasional multinucleated giant cells (figures 1 and 2) Special stains for tubercle bacilli were negative and concentrates from the nodes were also negative for tubercle bacilli Similar lesions were present in the sternal bone marrow (figures 3 and 4) All marrows

showed complete replacement of the fat by hematopoietic elements, the erythropoietic foci being markedly increased and erythroblasts and normoblasts dominating. The adrenal nodule was composed of typical, foamy, adult cortical cells. Sections from all of the other organs showed no significant changes.

*Pathological Diagnoses* Findings consistent with hemolytic anemia: (a) icterus, (b) erythroid hyperplasia of bone marrows, (c) erythroblastemia, (d) spherocytosis, (e) increased red cell fragility, (f) extra-medullary hematopoiesis of liver, kidney,

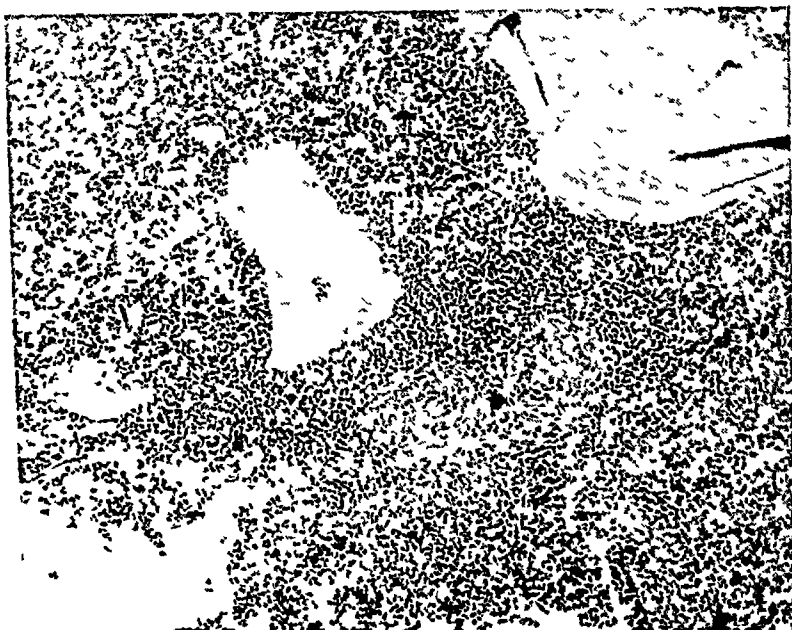


FIG 3 Bone marrow showing two tubercle-like lesions (sarcoid) similar to those of the lymph nodes. Hyperplasia is also evident in the replacement of the fat by hematopoietic elements. Note the numerous erythropoietic foci appearing as clumps of black dots. Phloxine methylene-blue  $\times 50$ .

lung and lymph nodes, cholelithiasis (pigment), Boeck's sarcoid with involvement of lymph nodes and bone marrow, accessory splenic tissue, cortical adenoma of adrenal.

### DISCUSSION

This case is typical, from the clinical, clinical-pathological and morphological findings, of hemolytic anemia. Whether it is of the congenital type with recurrence due to the small amount of accessory splenic tissue or of the acquired type and secondary to the sarcoidosis are points which may be debated. In any case it is of importance and interest.

The volume of splenic tissue was extremely small, totaling less than 20 cubic centimeters. This is of importance in consideration of the mechanisms postulated in the production of hemolytic anemia. Ham and Castle<sup>8</sup> have suggested that an important factor is stasis of blood in the spleen. In this case it is hardly conceivable that splenic stasis could be a factor when so little splenic tissue was present. We feel that if this case is to be regarded as the congenital type it presents strong evidence against the theory of stasis. On the other hand, one may readily conceive even a minute amount of tissue pro-

ducing the hemolysins that Dameshek and Schwartz<sup>9</sup> have described or the lysolecithins of Bergenheim and Fahraeus<sup>10</sup>

We believe that the case is of the acquired type and is secondary to the Boeck's sarcoid. The lesions with collagenous necrosis, monocytes, fibroblasts, giant cells and the absence of tubercle bacilli are typical of sarcoid. The occurrence of the lesions of sarcoid in the various organs of the body including the lymph nodes and bone marrow has been described by Nickerson<sup>11</sup>. The diagnosis of sarcoid is substantiated by the increase in globulin (4.0) with a total protein of 7.6 gm. This occurrence of hyperglobulinemia is of particular im-

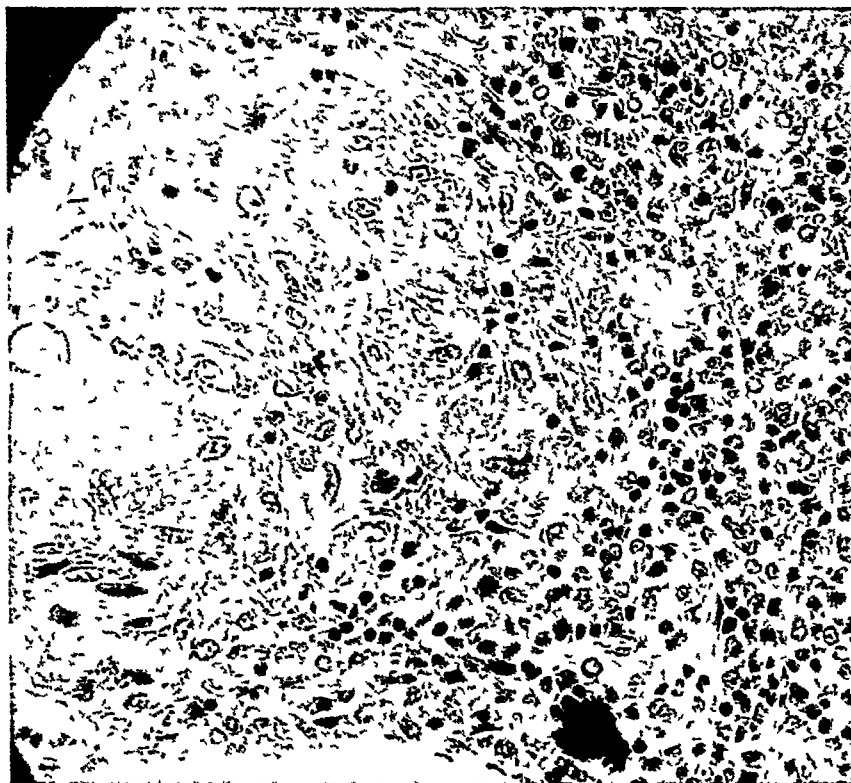


FIG 4 Bone marrow showing the detail of the sarcoid lesions under higher magnification  
Phloxine methylene-blue  $\times 970$

portance inasmuch as there have been previous reports of hemolytic anemia with hyperglobulinemia. Jeghers and Selesnick<sup>6</sup> reported a case, but no studies were done on their patient with reference to a possible diagnosis of sarcoid. However, the case reported by Kracke and Hoffman<sup>5</sup> as "chronic hemolytic anemia with autoagglutination and hyperglobulinemia" adds to the significance of our findings. Their case was a 32 year old female with a five year history of fleeting arthritis, the joints being painful but not swollen. She had anemia, reticulocytosis and erythroblastic crises. The red cell fragility was normal but there was "suggestive spherocytosis". The total protein was 9.14 gm with an albumin of 3.78 and a globulin of 5.26. Splenectomy was done but there was recurrence with an erythroblastic crisis and death. The autopsy was limited to a small incision but the findings in the liver are of particular interest.

"The liver weighed 2,000 gm. There was marked general atrophy of the hepatic cells with a small amount of fatty change. A single localized lesion having epithelioid cells, giant cells and a small amount of caseation necrosis was found. This resembled a miliary tubercle but acid-fast stains did not reveal organisms." The small granulomatous area was considered to be evidence of "chronic infection." They considered the case as an atypical chronic hemolytic anemia with autoagglutination and hemolysis secondary to chronic infection. The resemblance of the lesion to sarcoid was pointed out by the authors.

Hyperglobulinemia is a frequent finding in Boeck's sarcoid according to Middleton,<sup>12</sup> and the work of Harrell and Fisher<sup>13</sup> showed an increase in the total protein, particularly of the globulin fraction, often with reversal of the albumin-globulin ratio. We believe that the increase in globulin occurring in the case of Kracke and Hoffman<sup>5</sup> and our own is due to sarcoidosis and *not* the hemolytic anemia and that this may also be the explanation of the hyperglobulinemia occurring in the case of Jeghers and Selesnick.<sup>6</sup> We believe this because of the infrequency of hyperglobulinemia in hemolytic anemia and its frequent occurrence in sarcoidosis.

Haden<sup>7</sup> has described a case of hemolytic anemia secondary to sarcoid. The diagnosis of sarcoid was based upon radiological findings in the lungs, but its validity is open to question because of the uncertainty of the roentgenographic diagnosis of sarcoid and also because of the disappearance of the lesions after radio-therapy which is not the usual history of sarcoid. If Haden's case is accepted along with the one of Kracke and Hoffman and our own case, an association between Boeck's sarcoid and hemolytic anemia is indicated. However, it must be pointed out that in the acquired forms of hemolytic anemia there must be an additional intrinsic factor or abnormality as yet undetermined, for hemolytic anemia is an infrequent complication of any of the diseases that have been described as a precipitating cause.

### CONCLUSIONS

- 1 A case of hemolytic anemia is reported with recurrence after splenectomy and death in an erythroblastic crisis, associated with hyperglobulinemia and Boeck's sarcoid with involvement of the lymph nodes and bone marrow.
- 2 Sarcoidosis is added to the list of conditions which may produce a hemolytic anemia of the acquired type.
- 3 Hyperglobulinemia occurring with hemolytic anemia is probably due to sarcoidosis rather than to the anemia.

We are indebted to Dr. Reuben Ottenberg of New York City for making available to us the findings on the patient while she was under observation in New York and to Dr. Paul Klemperer of the Mt. Sinai Hospital of New York City for allowing us to review the sections of the spleen. We are also indebted to Dr. Franklin Fite of the U. S. Public Health Service, Marine Hospital, Norfolk, Virginia for the photomicrographs.

### BIBLIOGRAPHY

- 1 MINKOWSKI, O. Über eine hereditäre, unter dem Bilde eines chronischen Icterus mit Urobilinurie, Splenomegalia, etc., Verhandl. d. Kongr. f. inn. Med., Wiesbaden, 1900, LVIII, 316-318.

- 2 DAMESHEK, W Medical Progress Hematology Anemia, with particular reference to the hemolytic syndrome, New England Jr Med, 1942, ccxxvi, 339-346
- 3 SINGER, K, and DAMESHEK, W Symptomatic hemolytic anemia, Ann Int Med, 1941, xv, 544-563
- 4 WINTROBE, M Clinical hematology, 1944, Lea and Febiger, Philadelphia, pp` 394-395
- 5 KRACKE, R R, and HOFFMAN, B J Chronic hemolytic anemia with autoagglutination and hyperglobulinemia, Ann Int. Med, 1943, xix, 673-684
- 6 JEGHERS, H, and SELESNICK, S Hyperproteinemia, its significance, Internat Clin, 1937, iii, 248-275
- 7 HADEN, R L Principles of hematology, 1939, Lea and Febiger, Philadelphia
- 8 HAM, T H, and CASTLE, W B. Studies on destruction of red blood cells, Proc Am Philos Soc, 1940, lxxxii, 411-419
- 9 DAMESHEK, W, and SCHWARTZ, S O The presence of hemolysins in acute hemolytic anemia, New England Jr Med., 1938, ccxviii, 75-80
- 10 BERGENHEM, B, and FAHRAEUS, R. Über spontane Hämolysinbildung im Blut, unter besonderer Berücksichtigung der Physiologie der Milz, Ztschr f d. ges exper Med, 1936, xcvi, 555-587
- 11 NICKERSON, D A Boeck's sarcoid, Arch Path, 1937, xxiv, 19-29
- 12 MIDDLETON, W S. Sarcoidosis, in Textbook of medicine (CECIL), 1944, W B Saunders and Co, Philadelphia, p 455
- 13 HARRELL, G T, and FISHER, S Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium and phosphatase values, Jr Clin Invest, 1939, xviii, 687

## EDITORIAL

### *POST-WAR MEDICAL EDUCATION*

THE sudden and unexpected end of World War II in August has given rise to a number of new problems in medical education which the medical schools and hospitals of this country were scarcely better prepared to meet than were industry and labor in general. Or more specifically, the following problems now confront us: (1) deceleration of the medical school program, (2) the admission of veterans to the medical schools, (3) post-graduate training of veterans who entered the medical service of the Army or Navy with hospital training inadequate to prepare them for the practice of medicine, and (4) clinical rehabilitation of older physicians and surgeons who, having held largely administrative positions in the Army or Navy, feel the need of refresher courses and active participation in clinical work before resuming their practice.

Under the Army Specialized Training Program and the Navy V-12 Program premedical students who qualified for such training were permitted only 18 to 20 months of college in which to complete the requirements for admission to medical school. This meant that many of the male students entering medical school during the war were 18 or 19 years of age, considerably younger than the average student entering medical school before the war. Furthermore, these youthful souls were at once plunged into an accelerated program of instruction whereby the four academic years of medical school were completed in three calendar years. It is certainly to the credit of these young men that they have maintained such a strenuous program as successfully as they have. Nonetheless, both students and faculty members are thoroughly in accord that deceleration of the medical school curriculum is highly desirable. The relatively long summer vacations of the pre-war era provided time for the students to "digest" the knowledge they had acquired, to make practical application of this knowledge by means of laboratory work or junior internships, and—of utmost importance to some—to earn money with which to defray the cost of their education. Deceleration must be contingent upon two factors, namely the termination of the Army and Navy contracts with the medical schools and the abolition of the 9-9-9 plan for house officers in hospitals with a return to the 12-month internship in order that dates for commencing internship might dovetail with dates of graduation from medical schools. The Navy plans to terminate the V-12 program in the very near future, at which time the Navy students will return to civilian life as members of the inactive reserve and will be thrown "on their own" financially. These men will not be eligible for financial assistance under the "G-I Bill of Rights" unless they have had ninety or more days of active service with the Navy before entering medical school. Such a ruling seems a perfectly fair one since the government has already financed their

medical education completely besides paying these men regular maintenance salaries. The same rule will apply to the members of the A S T P when and if the Army returns them to an inactive status. So far the Army has given no indication as to when this will be. A number of the medical students inactivated from the services may find themselves financially embarrassed and, unless deceleration of the medical curriculum can be accomplished reasonably soon in order to provide summer vacations in which to earn money, scholarship and private loan funds will be taxed to the limit.

The admission of veterans to medical schools should be expedited in every way possible, since the majority of veterans who had partially or completely satisfied premedical requirements before entering the service will return to civilian life two or three years older than the average premedical student at a comparable stage in his training before the war. In view of this age factor, it would seem distinctly unfair to the veterans for medical schools to stiffen their requirements for admission at the present time. Rather, they might expect to return to their pre-war requirements by 1948 when the majority of qualified veterans who desire a medical education will already have gained admission to medical school. This would apply in particular to those schools which required a bachelor's degree prior to the war. In the writer's opinion, such schools would gain in respect what they might lose in prestige by admitting students during the next two years on the basis of the minimal amount of premedical training that was permitted during the war. Surely everything should be done to facilitate the medical education of those men who not only gave up several years of their lives but in many instances risked their lives in the service of their country.

Perhaps the most acute problem at the moment is the question of post-graduate training for young physician veterans who entered the medical corps of the Army or Navy with hospital training inadequate to prepare them for the practice of medicine, in many instances after an internship of only nine months. Relatively few of these young physicians had sufficient clinical work while in the service; some found themselves in purely administrative positions, others were assigned to very restricted fields of "medical activity", and a number claim that they never actually saw a patient during their entire period of duty with the armed forces. These men will benefit little by didactic refresher courses. What they need is practical clinical experience in hospitals. To meet this need, the medical schools and hospitals are creating additional positions on the house staff, such as residencies and assistant residencies, externships, and fellowships exclusively designed for veterans. It is to be hoped that the "supply" of such positions will at least approximate the "demand". Veteran physicians who enter upon such a program of training are eligible for subsistence allotments under the G. I. Bill of Rights.

Lastly, we face the question of the "clinical rehabilitation" of older physicians and surgeons who have grown "rusty," as so many of them put it,



in largely administrative positions with the Army or Navy. For these men, refresher courses covering recent developments in diagnostic procedures, therapeutics, and operative technics will undoubtedly prove valuable, and such courses have been organized at a number of the larger medical centers. However, many of these older physicians will wish practical experience in hospitals before resuming their practice. All of us who have remained in civilian life during the war should do everything within our power to lend assistance to these most deserving individuals in the medical profession, the veteran physicians of World War II.

W H B

## REVIEWS

*Medical Education in the United States before the Civil War* By WILLIAM FREDERICK NORWOOD Foreword by HENRY E SIGERIST 487 pages, 24 × 16 cm University of Pennsylvania Press, Philadelphia 1944 Price, \$6 00

The author of this reference book, a medical historian, has done the history of American Medicine a great service by producing this absorbing, vivid, impartial and scholarly account of medical education in this country in the century before the Civil War

In his preface, the author states that the study is not intended to be a technical consideration of the early teaching of medicine, but a survey of the rise and progress of the American system of medical instruction and the institutions of medical learning up to the time of the Civil War He further states that it has been his intent to draw from obscurity many relatively unknown institutions While the following is the author's concluding sentence, it epitomizes his objective "Medical education in the United States, with all its ramifications, in the century before the Civil War, constitutes a significant and unique chapter in the social history of the country"

The work is divided into eight parts, the chapters of five of which describe in detail the various medical schools of the five geographic sections into which the author divided the country for purposes of his book The other three parts include the introduction, factors in early American medical education, and the evolution of the American system of medical education

Wartime standards of publication have been conformed to, but the type is clear and easily read There are no illustrations The bibliography is extensive and is divided into the following sections general work, journals, newspapers and society proceedings, and manuscripts, but does not include the college catalogues since reference is made to these in the text To facilitate reference, there is a general index and an index of personal names

The author's style is informal and interpretive in which he presents an integrated and delightful picture of a very important century of American medical education from a broad point of view

Every medical school library should have a copy of this book on its reference shelf Graduates of the schools described in detail will enjoy the factual and impartial presentation of the history of their respective schools This work will take its rightful place beside the important histories of other phases of American Medicine, and the author is to be congratulated upon his contribution

J E S

## BOOKS RECEIVED

Books received during September are acknowledged in the following section As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them

*Essentials of Clinical Allergy* By SAMUEL J TAUB, M D 198 pages, 23 5 × 15 5 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$3 00

*Plaster of Paris Technique in the Treatment of Fractures and Other Injuries* By T B QUIGLEY, Lt Col, M C, A U S 107 pages, 24 × 16 cm 1945 The Macmillan Company, New York Price, \$3 50

*Textbook of Obstetrics* Stander's 3rd Revision—represents the Ninth Edition of Williams' Obstetrics By HENRICUS J STANDER M D, F A C S 1,277 pages, 25 × 17 cm 1945 D Appleton-Century Company, New York Price, \$10 00

- A Handbook for Dissectors* 2nd Edition By J C BOILEAU GRANT, Prof of Anatomy, University of Toronto, and H A CATES, Assoc Prof of Anatomy, University of Toronto 390 pages, 19 × 12.5 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$2.50
- Handbook of Physiology and Biochemistry* By R J S McDOWALL, M D, D Sc, M R C P 898 pages, 21 × 15 cm 1945 The Blakiston Company, Philadelphia Price, \$6.00
- Recent Advances in Neurology and Neuropsychiatry* 5th Edition By W RUSSELL BRAIN, M A, D M (Oxon), F R C P, and E B STRAUSS, M A, D M (Oxon), F R C P 363 pages, 21 × 14 cm 1945 The Blakiston Company, Philadelphia Price, \$5.00
- How a Baby Grows* By ARNOLD GESELL, Ph D, M D 78 pages, 30.5 × 24 cm 1945 Harper & Brothers, New York Price, \$2.00
- What People Are A Study of Normal Young Men* By CLARK W HEATH In Collaboration with LUCIEN BROUHA, LEWIS W GREGORY, CARL C SELTZER, FRÉDÉRIC L WELLS, and WILLIAM L WOODS—The Grant Study, Department of Hygiene, Harvard University Preface by ARLIE V BOCK 141 pages, 21.5 × 14.5 cm 1945 Harvard University Press, Cambridge, Massachusetts Price, \$2.00
- Pulmonary Tuberculosis A Handbook for Students and Practitioners* By R Y KEERS, M D (Edin), F R F P S (Glas), and B G RIGDEN, M R C S (Eng), L R C P (Lond) With a Foreword by F. H. YOUNG, O B E, M D (Camb), F R C P (Lond), D P H 273 pages, 19 × 12.5 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$5.00
- A Text-Book of Pharmacognosy* Fourth Edition By GEORGE EDWARD TREASE, B Pharm, Ph C, F R I C, F L S Revised with the Assistance of H E STREET, B Sc, Ph D, Ph C, and E O'F WALSH, B Sc, A R I C, Ph C With Contributions by R BIENFANG, B S, M S, Ph D, H M. HIRST, M P S, F R H S, H O MEEK, Ph C, and A H WARE, Ph C 799 pages, 22 × 15 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$7.50

## COLLEGE NEWS NOTES

### DR CHRISTOPHER C SHAW, F A C P , APPOINTED EDUCATIONAL DIRECTOR, AMERICAN COLLEGE OF PHYSICIANS

Dr Christopher C Shaw, F A C P , formerly of Bellows Falls, Vermont, has been appointed, as of November 1, 1945, the Educational Director of the American College of Physicians, in accordance with resolutions of the Board of Regents, June 10, 1945, providing for the establishment of this post. Dr Shaw, under the Executive Secretary of the College, has immediately taken over the direction of the postgraduate courses, research fellowships, clinical fellowships, program for the aid of members returning from the Armed Services, and other educational features in the College program.

Dr Shaw was born in Chichester, New York, attended St Paul's School at Concord, New Hampshire, Yale University (Ph B, 1924), and graduated from the University of Maryland School of Medicine, Baltimore, in 1931. He is a diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine. He did postgraduate work at Johns Hopkins University, the University of Maryland, and the Harvard Medical School, the latter under a Commonwealth Fund Fellowship. His teaching experience includes appointments in his earlier career at St Paul's School, the University of Maryland School of Medicine, Johns Hopkins University School of Medicine, and the University of Vermont College of Medicine. His internship was spent at the University of Maryland Hospital, and he served one year as a resident at the Baltimore City Hospital, and eighteen months with the Metropolitan Life Insurance Company Sanatorium at Mt McGregor, New York. He was engaged in the practice of internal medicine at Bellows Falls, Vermont, and was pathologist at the Rockingham General Hospital there. He has published a number of articles in well recognized medical journals. He was at one time Secretary of the Medical Staff of the Rockingham Hospital Association, President of the Windham County Medical Society, and member of the House of Delegates of the Vermont State Medical Society. He is a Fellow of the American Medical Association, and has been a Fellow of the American College of Physicians since 1940. Early in the war he volunteered for active service in the Medical Corps of the U S Navy, and rose rapidly through the ranks of Lieutenant Commander, Commander, and Captain. He graduated from the Naval School of Aviation Medicine at Pensacola and served thereafter on its faculty, was designated a Flight Surgeon by the Bureau of Aeronautics of the Navy Department, and served as Senior Medical Officer at the U S Naval Auxiliary Air Station, Whiting Field, Milton, Florida. He later served as Senior Medical Officer and Flight Surgeon of the Aircraft Carrier U S S Solomons, and served in the combat zones of both the Atlantic and the Pacific. Upon his separation from active duty in the Navy, he was appointed to this important post as Educational Director of the College.

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### NEW LIFE MEMBERS OF THE COLLEGE

The announcement of the following new Life Members of the College is made with gratification.

Dr Samuel L Crow, F A C P , Asheville, N C  
Dr James F Anderson, F A C P , Los Angeles, Calif  
Dr Alexander S Wiener, F A C P , Brooklyn, N Y  
Dr Theodore L Squier, F A C P , Milwaukee, Wis  
Dr Frank W Otto, F A C P , Los Angeles, Calif

Before January 1, 1946, is the most propitious time for Fellows to take out Life Membership. Such fees are deductible on Federal income taxes which are undoubtedly at their peak. It is anticipated that there will be some reduction in the income tax rate for 1946, thus allowing a smaller deduction for such fees. Many Fellows of the College are at present paying between 25 and 45 per cent of their income to Federal taxes. Obviously, the saving on the Life Membership fee is higher at the present time than may be anticipated in the future.

#### ACP MEMBERS IN THE ARMED FORCES

Up to the time of the release of this news item, 1,928 Fellows and Associates of the American College of Physicians have served on active military duty during World War II. One not previously recorded was Dr. Eugene F. DuBois, FACP, New York City, who served in the Medical Corps of the U. S. Naval Reserve intermittently between October 15, 1942, and April 5, 1945.

The number of retirements from active duty is rapidly growing. Since the last publication of this journal the following members of the College have been reported retired or on terminal leave:

Frank M. Acree, Greenville, Miss. (Capt., MC, AUS), FACP  
 Walter P. Adams, Norfolk, Va. (Lt. Comdr., MC, USNR), FACP  
 William H. Allen, Washington, D. C. (Col., MC, USA), FACP  
 Frank J. Altschul, Long Branch, N. J. (Major, MC, AUS), FACP  
 Irving L. Applebaum, Newark, N. J. (Major, MC, AUS), FACP  
 Theodore L. Badger, Boston, Mass. (Lt. Col., MC, AUS), FACP  
 Robert S. Baldwin, formerly Marshfield, Wis., now Highland Park, Ill. (Lt. Col., MC, AUS, (Associate)  
 Glenn L. Barnum, Pasadena, Calif. (Lt. Comdr., MC, USNR), (Associate)  
 Clifton H. Berlinghof, Binghamton, N. Y. (Lt. Col., MC, AUS), FACP  
 Michael Bevilacqua, Woodhaven, L. I., N. Y. (Major, MC, AUS), FACP  
 Staige D. Blackford, Charlottesville, Va. (Lt. Col., MC, AUS), FACP  
 Elton R. Blaisdell, Portland, Maine (Lt. Col., MC, AUS), FACP  
 Rankin C. Blount, Lexington, Ky. (Major, MC, AUS), FACP  
 Louis H. Charney, Oklahoma City, Okla. (Major, MC, AUS), FACP  
 A. Henry Claggett, Jr., Philadelphia, Pa., and Moorestown, N. J. (Lt. Col., MC, AUS), (Associate)  
 Milton H. Clifford, Cambridge, Mass. (Lt. Col., MC, AUS), FACP  
 Darrell C. Crain, Jr., Washington, D. C. (Capt., MC, AUS), (Associate)  
 Casimir J. Czarnecki, Toledo, Ohio (Major, MC, AUS), FACP  
 Lester C. Feener, El Paso, Tex. (Major, MC, AUS), (Associate)  
 Ferdinand Fetter, Philadelphia, Pa. (Comdr., MC, USNR), FACP  
 Stephen A. Foote, Jr., Houston, Tex. (Major, MC, AUS), FACP  
 S. Charles Franco, Brooklyn, N. Y. (Major, MC, AUS), FACP  
 Lee Pettit Gray, St. Louis, Mo. (Major, MC, AUS), FACP  
 Burgess Lee Gordon, Philadelphia, Pa. (Lt. Col., MC, AUS), FACP  
 Joseph M. Hayman, Jr., Cleveland, Ohio (Col., MC, AUS), FACP  
 James A. Halsted, Dedham, Mass. (Major, MC, AUS), FACP  
 Harold J. Harris, New York, N. Y. (Lt. Comdr., MC, USNR), FACP  
 Ali Cornelius Johnson, Great Falls, Mont. (Major, MC, AUS), FACP  
 Carl August Johnson, Chicago, Ill. (Major, MC, AUS), (Associate)  
 Clarence E. Johnson, Long Beach, Calif. (Major, MC, AUS), FACP  
 Benjamin Juhar, Detroit, Mich. (Major, MC, AUS), FACP  
 Max J. Klainer, Stoneham, Mass. (Capt., MC, AUS), (Associate)

Charles Edward Kossmann, New York, N Y (Lt Col, MC, AUS), (Associate)  
 Harry C Kroon, Syracuse, N Y (Major, MC, AUS), F A C P  
 John W P Love, Willow Grove, Pa (Major, MC, AUS), F A C P  
 Edgar M McPeak, San Antonio, Tex (Major, MC, AUS), F A C P  
 William S Middleton, Madison, Wis (Col, MC, AUS), F A C P  
 William C Moloney, Boston, Mass (Major, MC, AUS), (Associate)  
 Adolph T Ogaard, New Orleans, La (Major, MC, AUS), F A C P  
 Richard Ellsworth Olsen, Pontiac, Mich (Lt Comdr, MC, USNR), F A C P  
 Samuel A Overstreet, Louisville, Ky (Lt Comdr, MC, USNR), F A C P  
 Emmet F Pearson, Springfield, Ill (Lt Col, MC, AUS), F A C P  
 Frank S Perkin, Detroit, Mich (Major, MC, AUS), F A C P  
 Elbert L Persons, Durham, N C (Lt Col, MC, AUS), F A C P  
 Stephen Reynolds, Santa Barbara, Calif (Major, MC, AUS), (Associate)  
 Nelson G Russell, Jr, Buffalo, N Y (Major, MC, AUS), F A C P  
 Christopher C Shaw, Philadelphia, Pa (Capt, MC, USNR), F A C P  
 Hugh P Smith, Greenville, S C (Lt Col, MC, AUS), F A C P  
 William Stein, New Brunswick, N J (Major, MC, AUS) (Associate)  
 Stuart R Townsend, Montreal, Que, Can (Wing Comdr, RCAF), (Associate)  
 Paul R Wilner, Washington, D C (Major, MC, AUS), (Associate)  
 Edward E Woldman, Cleveland Heights, Ohio (Lt Col, MC, AUS), F A C P

Some of these discharges are of a considerably passed date but have only now been reported. Members are urged to notify the Executive Offices, 4200 Pine Street, Philadelphia 4, Pa, promptly of their retirements, giving dates and changes of address

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#### CHANGES OF ADDRESS

Members of the College and subscribers to the ANNALS OF INTERNAL MEDICINE are urged to keep the Executive Offices of the College informed of all changes of address. Numerous copies of the journal are returned because members and subscribers have failed to notify the College of their change of location. This is largely applicable to those on military duty

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#### PUBLICATION OF THE A C P MEMBERSHIP ROSTER POSTPONED

The sudden end of the war rendered valueless biographical data collected from members in the case of its more than 1,900 members on active military duty, and likewise affected the activities of many civilian members connected with war activities. Furthermore, the addresses of the great majority of members on military duty have been rapidly changing, and it has been found impractical to publish either a new Roster or a Supplement to the 1943 Roster at this time. It is planned, however, to publish a complete Directory during 1946

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#### EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

The oral examination scheduled by this Board at San Francisco on October 15, 16, 17 had to be cancelled owing to the fact that no hotel accommodations could be obtained either for the Board or for the candidates

The next written examination is scheduled for February 18, 1946, in various cities, applications to be filed by December 1, 1945, with William A Werrell, M D, Assistant Secretary-Treasurer, 1 West Main Street, Madison 3, Wisconsin

## GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College library of publications by members are gratefully acknowledged

- Major Lewis Barbato, (MC), AUS, Associate, Denver, Colo—1 reprint, "The State Mental Hospital—An Educational Center"
- Dr Benjamin M Bernstein, F A C P, Brooklyn, N Y—1 reprint, "Neuro-Functional Spasm"
- Lt Comdr Albert H Douglas, (MC), USNR, F A C P, New River, N C—2 reprints, "Penicillin in Malignant Granulocytopenia" and "Mechanism of T Deflection in the Precordial Electrocardiogram"
- Lt Comdr Adolph M Hutter, (MC), USNR, F A C P, San Francisco, Calif—1 reprint, "The Transmission of Penicillin through the Placenta"
- Dr Arthur H Jackson, F A C P, Waterbury, Conn—1 reprint, "Electric Shock Therapy Its Use in a General Hospital"
- Comdr M J Matzner, (MC), USNR, F A C P, Brooklyn, N Y—2 reprints, "Postvaccinal (Yellow Fever) Jaundice" and "An Optical Fluorescence Comparator"

Acknowledgment is also made of the receipt of the *Collected Papers* from the Squibb Institute for Medical Research, New Brunswick, N J, Volume 3, 1943-44, Dr George A Harrop, F A C P, Director

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REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

*Major General George C Dunham Succeeds Nelson Rockefeller*

Major General George C Dunham, (MC), USA, F A C P, who has served in the Army Medical Corps since 1916, has submitted his resignation as President of the Institute of Inter-American Affairs and Deputy Director of the Office of Inter-American Affairs, owing to reasons of health. General Dunham will succeed Nelson A Rockefeller as Chairman of the Board of Directors of the Institute.

The General's book, "Military Preventive Medicine," has become a standard text. His fame as the "flying doctor of the Americas" is evidence of his average of 100,000 miles of airplane travel to visit more than 1,000 health, sanitation and food projects organized under his direction. For this contribution to inter-American relations, General Dunham was awarded the Distinguished Service Medal with a presidential citation in the early part of August. He also received national honors from the governments of Brazil, Bolivia, Nicaragua, Chile, Haiti, and Peru.

*Lieutenant Colonel Staige D Blackford Returns to University of Virginia*

Lt Col Staige D Blackford, (MC), F A C P, who served thirty months in Italy and North Africa as Chief of the Medical Service of the 8th Evacuation Hospital and for the past two months as Chief of the Medical Service at Valley Forge General Hospital, has recently returned to his civilian position of Associate Professor of Internal Medicine in the Department of Medicine at the University of Virginia. A resident of Virginia, Colonel Blackford served in World War I and was presented the Croix de Guerre by the French government.

*Promotion, Medical Corps*

Howard Avery Lindberg, F A C P, Chicago, Ill, has been advanced from Major to Lieutenant Colonel.

*Surgeon General Urges Prompt Release of Eligible Personnel*

Major General Norman T Kirk, F A C P , the Surgeon General of the Army, has expressed the desire that all commanding officers give the fullest possible co-operation towards effecting the early release of Medical Department personnel who are eligible for separation from the service under the announced policy

At the same time he urged that all Medical Department personnel who occupy key positions and who are eligible for separation under the present criteria volunteer to continue on active duty to assist in maintaining the present high standards of medical care if no replacement is immediately available. It is contemplated that a period of six months' duty will be sufficient time to allow for the arrival of a replacement or for training an officer to take over duties of key positions and thus allow all officers eligible for release to be returned to civilian life.

General Kirk requested that commanding officers make every effort to obtain replacements for Medical Department personnel eligible for release in order that those officers might be returned to civil life at the earliest possible moment.

Under the announced Medical Department demobilization policy, Medical and Dental Corps officers are eligible for release provided they meet any one of the following criteria:

- a Adjusted service score of 80 or above
- b 48 years of age to the nearest birthday or above
- c Entry on active duty prior to Pearl Harbor excepting critical specialists qualified in eye, ear, nose and throat, plastic surgery, orthopedic surgery, neuropsychiatry or laboratory clinicians. Officers qualified in these specialties are eligible for release if they entered on active duty prior to January 1, 1941, or if they meet the criteria on points or age.

This revised policy on separation is expected to return 13,000 physicians, 3,500 dentists, 25,000 nurses and a large number of other Medical Department officers to civilian life by the first of the year.

It will be necessary to retain a large number of low score men in the service for replacement for overseas men having high ASR scores. Other low score men must of necessity be retained in the service to carry on the necessary activities of the Medical Department in this country and in theaters where American troops are operating.

It is intended that no one eligible for release will be held in the Army because there are men with higher scores overseas who have not been returned home. Eligible men will be discharged as rapidly as they can be processed for separation.

No enlisted personnel with a sufficient number of critical points will be kept because of "military necessity" except those very few men classified in one of three essential technical skills. These are Orthopedic mechanics, electro-encephalographers who operate electrocardiac equipment and radio transmitter attendants. The latter is not in the Medical Department.

*Total Streptomycin Production Only Fourteen Ounces a Month*

The War Department said recently that streptomycin, the new wonder sister drug to penicillin, was being used in thirty Army general hospitals over the country, but that it was so difficult to obtain that the total output of the four companies now making it has been only fourteen ounces a month.

The Army is receiving many requests for the drug for use in treatment of urinary and other infections caused by gram-negative bacteria which do not respond to penicillin, but these cannot be met since the Army neither controls the supply nor can get enough for its own needs in treatment of battle-wounded soldiers.

General Kirk said that the four companies, Merck, Upjohn, Abbott and Squibb,



were the principal manufacturers of the new product, but that other concerns were working at experimental production at pilot plants and that any civilian request for streptomycin naturally would go to these companies

A gram, or 1,000,000 units, is the standard daily dose administered in three injections over a twenty-four hour period

Production is limited severely because the drug is obtained from a natural fungus found in the soil and must be grown under carefully controlled laboratory conditions which cannot be hurried

The phenomenal production of penicillin which brought it from a laboratory curiosity to a commonly-used drug and the price from astronomical figures to about a dollar a dose was due in part to pressure of wartime needs

The Surgeon General explained that the Army's principal needs are for treatment of soldiers with severed spinal cords who develop urinary tract infections because of a loss of bladder function, and to some extent in treating some cases of meningitis and other infections which do not respond readily to penicillin therapy

#### MEMBERS INVITED TO REPORT OPENINGS FOR DOCTORS TO THE COLLEGE

Members of the College will perform a service by reporting to the Educational Director of the College, Dr Christopher C Shaw, 4200 Pine Street, Philadelphia 4, Pa, openings that might be filled by Associates and Fellows returning to civilian life from military service. There are a number of College members well qualified for teaching in the various fields of internal medicine, for residencies, and for private or group practice. The Educational Director's office will be pleased to act as a medium of contact. The College program calls for an active and effective service to its members returning to civilian life

Dr Wallace M Yater, for many years Professor of Medicine at Georgetown University School of Medicine, Washington, D C, has resigned that post as of October 27, 1945

Dr Yater received his A B degree from George Washington University, his M D degree from Georgetown, and his Master of Science degree from the Mayo Foundation of the University of Minnesota. He has been a Fellow of the College and its Governor for the District of Columbia for several years. He has devoted twenty-one years to the field of medical education, and has been head of the Department of Medicine at the Gallinger Municipal Hospital for thirteen years. He is a diplomate of the American Board of Internal Medicine, with special certification in cardiovascular disease. He is Past Chairman of the Section on Experimental Medicine and Therapeutics of the American Medical Association, Past Chairman, Section for the Study of the Peripheral Circulation, American Medical Association, member, Committee on Medicine, National Research Council, and member of its Subcommittee on Cardiovascular Diseases, member, American Society for Clinical Investigation, Director, American Heart Association, member, Sigma Xi, Editor, Medical Annals of the District of Columbia, author of approximately 150 published articles on medical subjects (mainly original contributions to medical science) and 2 medical textbooks, deliverer of a Koher Memorial Lecture, a Mayo Foundation Lecture, and many medical addresses the country over. During his tenure as Associate Professor of Medicine and Professor of Medicine, he has trained approximately forty-five Fellows in Medicine as well as directed the Department of Medicine

Dr Frank H Krusen, F A C P, Director of the Baruch Committee on Physical Medicine has announced the appointment of Colonel Howard A Rusk, F A C P, (MC), AUS, formerly of St Louis, as Consultant on Physical Rehabilitation for the

Baruch Committee Colonel Rusk, whose pioneering work as Chief of the Convalescent Division of the Air Surgeon has attracted national attention, will make his headquarters at the New York office of the Committee created a year ago by Bernard M Baruch

Colonel Rusk has resigned from the Army to serve the Committee temporarily in endeavoring to apply his Army experience in physical rehabilitation to the urgent civilian needs in this phase of physical medicine

Dr Milford Leroy Hobbs, F A C P, formerly of Burlington, Vermont, last July 1 became Pathologist and Director of the Laboratory of the Fairmont General Hospital at Fairmont, West Virginia

Dr William Herschel Allen, F A C P, has retired from the Medical Corps of the Regular U S Army, effective September 30, 1945, and has entered the practice of internal medicine on the staff of the Santa Barbara Clinic at Santa Barbara, California

#### A C P POSTGRADUATE COURSES, AUTUMN SCHEDULE

The entire group of seven courses scheduled between October 8 and December 1, 1945, have been oversubscribed in every instance Never before has the demand for these courses been so great The College was able to accommodate but a small percentage of non-members in the courses but a special effort was made to accommodate as many as possible of the medical officers recently separated or soon to be separated from the military services

The College is preparing an extended schedule of courses for the spring of 1946 The Educational Director will appreciate receiving suggestions of courses most desired, and he will attempt to arrange them where possible

For the information of members of the College and readers of this journal, we publish hereafter the outline of the course in Advanced Cardiology given at the Philadelphia General Hospital, November 26-December 1, since it was not previously published in these pages

#### COURSE No 7—ADVANCED CARDIOLOGY

(November 26-December 1, 1945)

*Philadelphia General Hospital, Philadelphia, Pa*

THOMAS M McMILLAN, M D, F A C P, *Director*

#### *Officers of Instruction*

Oscar V Batson, M D, Professor of Anatomy, University of Pennsylvania Graduate School of Medicine

Samuel Bellet, M D, F A C P, Associate in Cardiology, University of Pennsylvania Graduate School of Medicine, Assistant Chief, Cardiology, Philadelphia General Hospital

Henry L Bockus, M D, F A C P, Professor of Gastroenterology, University of Pennsylvania Graduate School of Medicine

W Edward Chamberlain, M D, F A C P, Professor of Radiology, Temple University School of Medicine

Julius Comroe, Jr, M D, F A C P, Assistant Professor of Pharmacology, University of Pennsylvania School of Medicine

William Dock, M D, F A C P, Professor of Medicine, Long Island College of Medicine, New York, N Y

- Robert Dripps, M D, Assistant Professor of Anesthesiology and Associate in Pharmacology, University of Pennsylvania School of Medicine
- Thomas M Durant, M D, F A C P, Associate Professor of Internal Medicine, Temple University School of Medicine
- Mary H Easby, M D, F A C P, Assistant Clinical Professor of Medicine, Woman's Medical College of Pennsylvania, President, Philadelphia Heart Association
- Harrison F Flippin, M D, F A C P, Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine
- Harry Gold, M D, Associate Professor of Pharmacology, Cornell University Medical College, New York, N Y
- Benjamin Gouley, M D, Chief Coroner's Physician, City of Philadelphia
- John Q Griffith, Jr, M D, F A C P, Associate in Medicine and A Atwater Kent Fellow in Medicine, University of Pennsylvania School of Medicine
- Seymour Kety, M D, Associate in Pharmacology, University of Pennsylvania School of Medicine
- David W Kramer, M D, F A C P, Assistant Professor of Medicine, Jefferson Medical College of Philadelphia
- William G Leaman, Jr, M D, F A C P, Professor of Medicine, Woman's Medical College of Pennsylvania
- Alexander Margolies, M D, F A C P, Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine
- Thomas M McMillan, M D, F A C P, Associate Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, Chief, Cardiology, Philadelphia General Hospital
- Herman Ostrum, M D, Radiologist, Philadelphia General Hospital, Assistant Professor of Radiology, University of Pennsylvania Graduate School of Medicine
- Rufus S Reeves, M D, F A C P, Director, Department of Public Health of Philadelphia
- Major George P Robb, (MC), AUS, F A C P, Walter Reed General Hospital, Washington, D C, Assistant Medical Director, Metropolitan Life Insurance Company, New York
- Ella Roberts, M D, F A C P, Medical Director, Children's Heart Hospital of Philadelphia
- Hugo Roesler, M D, F A C P, Assistant Professor of Radiology, Temple University School of Medicine, Cardiologist, Department of Medicine, Temple University Hospital
- Isaac Starr, M D, Milton Bixler Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine
- William D Stroud, M D, F A C P, Professor of Cardiology, University of Pennsylvania Graduate School of Medicine
- Helen Taussig, M D, Pediatrician, Johns Hopkins Hospital, Associate in Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md
- Edward Weiss, M D, F A C P, Professor of Clinical Medicine, Temple University School of Medicine
- Charles C Wolferth, M D, F A C P, Professor of Clinical Medicine, University of Pennsylvania School of Medicine

### *Outline of Course*

*Monday, November 26*

A M. Session

9 15- 9 30 Registration

9 30- 9 45 Welcome and Announcements

Dr Rufus S Reeves, Director, Department of Public Health  
of Philadelphia

- 9 45-10 45 Some of the Newer Conceptions of Congestive Heart Failure  
Dr Starr
- 10 45-11 00 Recess
- 11 00-12 00 The Physiology, the Diagnosis and the Treatment of the More  
Important Congenital Malformations of the Heart  
Dr Taussig
- 12 00- 2 00 Recess
- P M Session
- 2 00- 3 00 The Principles underlying Electrocardiography  
Dr Wolferth
- 3 00- 4 00 The Physiology, the Diagnosis and the Treatment of the More  
Important Congenital Malformations of the Heart (con-  
cluded)  
Dr Taussig
- 4 00- 4 10 Recess
- 4 10- 4 45 Air Embolism Some of Its Effects upon the Heart and Its Treat-  
ment  
Dr Durant
- 5 00 Cocktail Party  
Headquarters, American College of Physicians, 4200 Pine  
Street

*Tuesday, November 27*

## A M Session

- 9 00-10 00 Acute Pericarditis  
Dr McMillan
- 10 00-10 45 Roentgen Findings in Pericarditis  
Dr Ostrum
- 10 45-11 00 Recess
- 11 00-12 00 Heart Sounds  
Dr Margolies

## 12 00- 2 00 Recess

## P M Session

- 2 00- 3 00 Roentgen Findings in the Lungs in Heart Disease  
Dr Roesler
- 3 00- 4 00 Oxygen in the Treatment of Circulatory Disease  
Dr Comroe
- 4 00- 4 10 Recess
- 4 10- 5 00 Syncope of Cardiac Origin  
Dr Bellet

*Wednesday, November 28*

## A M Session

- 9 00- 9 30 The Importance and the Public Health Aspects of Rheumatic Fever  
Dr Stroud
- 9 30-10 00 The Use of the Sulpha Drugs in Rheumatic Fever  
Dr Roberts
- 10 00-10 50 The Psychosomatic Aspects of Cardiovascular Disease  
Dr Weiss
- 10 50-11 00 Recess
- 11 00-12 00 The Principles Underlying Electrocardiography (continued)  
Dr Wolferth
- 12 00- 2 00 Recess

## P M Session

- 2 00- 2 55 Some of the Newer Methods of Studying the Circulation  
Dr Kety
- 2 55- 3 55 Predilection of Atherosclerosis for the Coronary Arteries  
Dr Dock
- 3 55- 4 05 Recess
- 4 05- 5 00 The Effects of Drugs upon the Heart  
Dr Starr

*Thursday, November 29*

## A M Session

- 9 00-10 00 Electrocardiography Brief Considerations of
- (1) The Use of Large Doses of Quinidine in the Treatment of Ventricular Paroxysmal Tachycardia Following Myocardial Infarction
  - (2) Electrocardiographic Patterns Simulating Myocardial Infarction
  - (3) Dissecting Aneurysm Rupturing into the Pericardium
- Dr McMillan and Dr Bellet
- 10 00-10 45 Some of the Causes of Sudden Death as Seen by a Coroner's Physician  
Dr Gouley
- 10 45-11 00 Recess
- 11 :00-12 00 Cardioangiography  
Major Robb

12 00- 2.00 Recess

## P M Session

- 2 00- 3 00 Digitalis and Some of the Newer Glycosides  
Dr Gold
- 3 00- 3 55 A New Roentgen Method of Determining the Amplitude of Cardiac Contraction  
Dr Chamberlain
- 3 55- 4 05 Recess
- 4 05- 5 00 The Heart and Anesthesia  
Dr Driggs

*Friday, November 30*

## A M Session

- 9 00- 9 55 The Medical Treatment of Hypertension  
Dr Griffith
- 9 55-10 55 The Principles Underlying Electrocardiography (concluded)  
Dr Wolfarth
- 10 55-11 05 Recess
- 11 05-12 00 Heart Sounds (concluded)  
Dr Margolies

12 00- 2 00 Recess

## P.M Session

- 2 00- 3.00 The Ballistocardiograph as a Clinical Instrument  
Dr Starr
- 3.00- 3.50 Some of the Important Features of Cardiac Anatomy  
Dr Batson.
- 3 50- 4 00 Recess

## 4 00- 5 00 Question and Answer Period

Dr Leaman, Leader, Drs Bellet, Durant, Easby, Kramer, Margolies, McMillan, Roesler, Stroud and Wolferth

*Saturday, December 1*

9 00-10 00 (1) A Critical Consideration of the Roentgen Methods of Determining Heart Size

(2) Roentgen Findings in Disease of the Aorta

Dr Roesler

10 00-10 50 Results of the Newer Treatment of Bacterial Endocarditis

Dr Flippin

10 50-11 00 Recess

11 00-12 00 The Relationship of Cardiovascular and Gastrointestinal Symptoms  
Dr. Bockus

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Lieutenant Colonel James E Cottrell (MC), F A C P, was recently made Chief of Medical Service at the Lovell General Hospital, Fort Devens, Massachusetts, succeeding Colonel Julien E Benjamin, F A C P, who has been separated from the Army and returned to Cincinnati. It is anticipated that Colonel Cottrell may also be separated from the service in the near future and will return to the practice of Internal Medicine in Philadelphia.

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Captain Richard A Kern, F A C P, Philadelphia, Chief of Medicine at the Philadelphia Naval Hospital, was recently promoted from Captain to the rank of Commodore

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Dr Maynard E Holmes, F A C P, Professor of Clinical Medicine at Syracuse University College of Medicine, gave a graduate lecture before the Broome County Medical Society at Binghamton, N Y, on October 9, 1945, on "The Management of Diabetes with the Newer Forms of Insulin" The meeting was arranged by the Committee on Public Health and Education of the New York State Medical Society

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Mead Johnson and Company, Evansville, Indiana, publishes annually a catalogue of medical books published during the year, their last edition being "Medical Books Published During 1944" This publication has been especially timely and valuable during the war years, particularly among countries in Europe where they have been cut off from contact with the publication of medical books in the United States This publication also is valuable to returning medical officers from the armed forces and of interest to many civilian physicians

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#### DR POTTENGER MARKS THREE ANNIVERSARIES AT MONROVIA

Dr Frank M Pottenger, F A C P, founder of the Pottenger Sanitarium at Monrovia, celebrated on September 27 a three-way anniversary—his 42nd anniversary of the founding of the sanitarium, his 50th anniversary of his going to California to practice medicine, and his 76th birthday Dr Pottenger is a past President of the American College of Physicians and has been an active Fellow practically from its conception He is just completing a new book on "Clinical Tuberculosis"

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Dr Stuart R Townsend (Associate) has retired as Wing Commander, Royal Canadian Air Force, and has returned to the faculty of McGill University and to the Attending Staff of the Montreal General Hospital

Dr Harold J Harris, F A C P, has been retired from active naval service and has returned to his offices at Westport, Essex County, New York. Much of his time will be devoted to clinical research in brucellosis in New York.

During November he delivered a series of lectures on brucellosis at the University of Cordoba, Argentina.

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Dr J C Geiger, F A C P, Director of Public Health of the City and County of San Francisco, was recently granted the Supreme Decoration of the Order of Merit of Juan Pablo Duarte, grade of Knight Commander, Dominican Republic, "for distinguished service in public office as Director of a noteworthy and alert Department of Health and as a civic statesman in the field of foreign affairs."

Juan Pablo Duarte, the patriot after whom this decoration is named, in 1844 overwhelmed the enemies of his country and with others established the Dominican Republic.

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#### PHYSICIAN-ARTISTS' PRIZE CONTEST

The American Physicians Art Association, with the cooperation of Mead Johnson & Company, is offering an important series of War (Savings) Bonds as prizes to physicians in the armed services and also physicians in civilian practice for their best artistic works depicting the medical profession's "skill and courage and devotion beyond the call of duty."

For full details, write to the Association's Secretary, Dr F H Redewill, Flood Bldg, San Francisco, Calif, or Mead Johnson & Co, Evansville 21, Ind. Also pass this information on to your physician-artist friends, both civilian and military.

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The New York Academy of Medicine is conducting its 20th series of Friday afternoon lectures, held at the Academy, 4 30 o'clock. Among speakers and their subjects are the following: December 7—Senescence of the myocardium—presbycardia—William Dock, F A C P, Professor of Medicine, Long Island College of Medicine, December 14—The therapeutic and toxic actions of some drugs recently introduced in the treatment of cardiac disorders—Arthur C DeGraff, F A C P, Samuel A Brown Professor of Therapeutics, New York University College of Medicine, January 4—Current views of rheumatic diseases and their management—Richard H Freyberg, F A C P, Associate Professor of Clinical Medicine, Cornell University Medical College, Director of Department of Internal Medicine, Hospital for Special Surgery, January 18—Apical systolic murmurs in incipient rheumatic heart disease—Captain Arthur M Master (MC), USNR, F A C P, Cardiologist, U S N H, St Albans, Long Island.

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Dr Hobart A Reimann, Professor of Medicine, Jefferson Medical College, Philadelphia, has just returned from a 2 months' expedition to Chungking, China, as a member of a team to aid in the control of an epidemic of cholera. The project was sponsored by the United Nations Relief and Rehabilitation Administration at the request of the U S Army and the Chinese National Government.

There were 9 members of the Commission, 1 clinician, 1 bacteriologist, several public health experts and sanitary engineers. The Commission arrived in Chungking late in July after the peak of the epidemic had passed. About 2,500 cases were registered but many more undetected ones occurred.

## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

December 7—Emotional Factors in Physical Illness—Dr Earl D Bond

December 28—Difficulties in the Diagnosis of Surgical Lesions of the Upper Urinary Tract—Dr Leon Herman

REGION No 23 (Nevada, Northern California)—Dr S R Mettier, Chairman, Dr E H Falconer, Dr D N Richards

*Station Hospital, Camp Stoneman, Pittsburg, California*

November 17—Plastic Surgery—Dr George Pierce

December 15—Diagnosis and Treatment of Abnormal Mechanisms of the Heart—Dr William J Kerr

*Hammond General Hospital, Modesto, California*

November 21—The Use of Penicillin in Injuries and Infections—Dr Horace J McCorkle

*ASF Regional Station Hospital, Oakland, California*

December 12—Nephritis—Dr Thomas Addis

*Station Hospital, Fort Ord, California*

November 17—Diseases of the Thyroid Clinical Diagnosis and Management—Dr Mayo H Soley

December 15—Diseases of the Lungs and Their Treatment—Dr Philip H Pierson

*U S Naval Hospital, Treasure Island, California*

November 16—Interpretation and Misinterpretation of Certain Laboratory Tests—Dr James Hopper

December 7—Diagnosis of Atypical Anemias—Dr Stacy R Mettier

*Station Hospital, Camp Roberts, California*

December 8—Diseases of the Thyroid Clinical Considerations—Dr Mayo H Soley

*Station Hospital, Chico Army Air Base, Chico, California*

December 6—Laboratory Aids in the Diagnosis of Disease—Dr Jesse L Carr

*Station Hospital, Stockton Air Field, Stockton, California*

December 12—The Fundamentals of Endocrine Diagnosis—Major Roberto F Escamilla

REGION No 24 (Southern California)—Lt Comdr G C Griffith, Chairman, Capt H P Schenck, Dr J Churchill, Dr W Morrison, Maj N Nixon

*Birmingham General Hospital, Van Nuys, California*

November 28—Thoracic Surgery—Captain W L Rogers

December 12—Recent Developments in Diabetes—Dr Howard F West

December 26—Neuro-Surgery—Captain Everett Dickinson

*ASF Regional Hospital, Camp Haan, California*

December 4—Reconstruction Problems—Captain Fraser L MacPherson



*AAF Regional Station Hospital, March Field, California*

November 20—Compound Fractures—Commander P E. McMasters  
 December 18—Acute Nephritis—Dr Lyttle

*Station Hospital, Camp Cooke, California (afternoon session) and Hoff  
 General Hospital, Santa Barbara, California (evening session)*

November 21—Pericarditis—Lieutenant C Sylvester McGinn  
 December 5—The Cancer Problem in Service Personnel—Lieutenant J S Binkley  
 December 19—Problems in Tuberculosis—Commanders W L Rogers and A W. Hobby

*Torney General Hospital, Palm Springs, California*

November 20—Peptic Ulcer—Dr William Boeck  
 December 4—The Rh Factor—Captain George Macer  
 December 18—Hemolytic Streptococcal Respiratory Infections and Their Sequelae—  
 Dr Robert E Solley

*U S Naval Hospital, Santa Margarita Ranch, Oceanside, California.*

November 22—Modern Concepts of Leprosy—Dr Maxmillian Obermayer  
 December 13—Communicable Diseases—Major Norman Nixon  
 December 27—Problems Associated with the Surgery of the Biliary Tract—Captain  
 Howard K Gray

*U S Naval Hospital, Long Beach, California*

November 21—Liver Disease—Captain John Ruddock  
 December 19—Low Back Pain—Major Samuel Weaver

*U S. Naval Hospital, Corona, California*

November 22—Tumor Pathology—Dr Edward Butt  
 December 13—The Streptococcal Problem—Lieutenant Commander George R Underwood  
 December 27—The Use of Products of Fibrinogen and Thrombin on Otolaryngology  
 —Captain Harry P Schenck.

*U S Naval Air Training Station, San Diego, California*

December 7—Burns—Captain H T D Kirkbaum  
 December 21—The Penicillin Treatment of Syphilis and Gonorrhea—Commander W W Duemling

*AAF Regional and Convalescent Hospital, Santa Ana Army Air Base, California*

November 20—The Use of Products of Fibrinogen and Thrombin in Otolaryngology  
 —Captain Harry P Schenck  
 December 4—Contagious Diseases—Commander R A Trombley  
 December 18—Compound Fractures—Commander P E McMasters

*U S. Naval Hospital, San Diego, California*

December 6—The Classification and Diagnosis of the Anemias—Dr A G Foord.

*U. S. Regional Hospital, Pasadena, California*

December 10—The Rh Factor—Captain George Macer.

## FELLOWSHIPS OFFERED BY THE AMERICAN COLLEGE OF PHYSICIANS

*Research Fellowships*

The American College of Physicians has resumed its Research Fellowships in Medicine, which were discontinued during the War. These fellowships, limited in number, are designed to provide an opportunity for research training either in the basic medical sciences, or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory in which he has chosen to work and that the laboratory will supply the facilities necessary for the proper pursuit of the research. The term of appointment is for one year. The fellowship stipend will be from \$1,800 00 to \$2,500 00 per annum.

*Clinical Fellowships*

In order to assist in providing opportunities for postgraduate education in Internal Medicine for medical officers discharged from the Armed Forces, the American College of Physicians has established a limited number of Clinical Fellowships in Medicine for 1946. These fellowships are available for physicians honorably discharged from the Armed Forces who are Fellows, Associates or prospective candidates for Associateship in the College. They are designed to provide opportunity for advanced clinical training in Internal Medicine, or in any of its special fields. They are limited to a term of one year, may start at any time during 1946, and will not be renewable. Assurance must be provided that the applicant will be acceptable in the clinic in which he has chosen to work. The fellowship stipend will ordinarily be from \$1,800 00 to \$3,000 00, depending on individual circumstances.

Application forms for these fellowships will be supplied on request to the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. Decision with respect to award of a fellowship will be made and the applicant notified of the action taken as soon as possible after receipt of the application and review by the Committee on Fellowships and Awards.

## SPECIAL NOTICES

## COMMITTEE ON GROWTH OF THE NATIONAL RESEARCH COUNCIL

The appointment of a "Committee on Growth," with membership designed to be broadly representative of the fields concerned in cancer research, both basic and clinical, has already been announced by the National Research Council of the National Academy of Sciences. The Committee was created, within the Division of Medical Sciences of the Council, as a result of action by the American Cancer Society designating the Academy as its scientific advisor for research.

The Committee wishes to call the attention of interested investigators to the general outline of endeavor which it proposes to foster and the general principles by which it will be guided. The Committee accepts the interpretation of its field of interest as including reliance on, contact with and support of research in the basic sciences bearing broadly on the whole phenomenon of growth.

The Committee has adopted the following major principles by which, in so far as possible, it will be guided in its sponsorship of research and training programs:

- (a) Desirability of long-term grants to projects of major importance
- (b) Grants, where possible, of such magnitude as to permit individual investigators to appoint associates for long-term training periods
- (c) Granting of fellowships to institutions for training of workers to acquire new techniques and wider experience

- (d) Maintenance of continuing individual contact with workers in field
- (e) Provision, on a participating basis, for continuing economic security for professional workers
- (f) Liberal attitude toward the investigator's work, his publication and reports

To assist it in the fulfillment of its advisory functions the Committee, on its part, will make free use of either *ad hoc* or standing subcommittees in specific fields of interest. Furthermore, it proposes to arrange conferences of competent groups for discussion of problems, for interchange of reports, etc., make surveys to analyze problems or to determine progress in areas of special interest pertaining to cancer, evaluate, through study by subcommittees and by the main committee, basic and clinical research undertakings, and submit recommendations for support to the American Cancer Society, initiate and plan broad or specific programs of basic and clinical research, through activities of the subcommittees and main committee, and secure the cooperative efforts of investigators in the general undertakings.

The Committee has established a central office in the Washington headquarters of the Council where information on all phases of cancer research will be assembled and from which reports may be distributed to interested investigators.

Many members of the Committee have participated intensively in the broad programs of research conducted under the pressure of war. It is both the hope and the sanguine expectation of the Committee that the fruitful pattern of cooperative investigations so successfully established during the war years, can now be carried on, modified and tempered to existing needs, into the continuing war against disease.

Membership of the Committee, as now constituted, includes the following

Dr C P Rhoads, *Chairman*  
 Dr Florence R Sabin, *Secretary*  
 Dr A R Dochez  
 Dr A Baird Hastings  
 Dr Charles B Huggins  
 Dr Donald F Jones  
 Dr C. C Little  
 Dr Carl R Moore  
 Dr John J Morton  
 Dr James B Murphy  
 Dr Eugene P Pendergrass  
 Dr Howard C Taylor, Jr  
 Dr M A Tuve  
 Dr. M C Winternitz

PHILIP S OWEN, M.D.,  
 For the Committee on Growth,  
 Division of Medical Sciences,  
 National Research Council,  
 2101 Constitution Avenue,  
 Washington 25, D C

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#### AN ABSTRACTING SERVICE FOR HUMAN BIOLOGY

The Trustees of *Biological Abstracts* announce the establishment, beginning in January, 1946, of a new section of *Biological Abstracts*—Section II, specially assembled Abstracts of Human Biology—intended for anthropologists, sociologists, psychologists, neurologists and psychiatrists, students of child development and human welfare, and students of man generally.

The new section will be an assemblage of all abstracts published in *Biological Abstracts* dealing with the broad field of human and social biology. Biological studies on human inheritance, on population and fertility, on endocrine and neurological factors affecting growth development and human personality, on alcoholism and drug addiction and on nervous disorders and mental deficiencies, and broad nutritional and epidemiological studies affecting human welfare, are some of the many fields that will be covered. The annual subscription price for the ten abstract issues, plus the complete index of the year's volume of *Biological Abstracts* will be \$6.00 (\$6.50 outside the United States).

Full information may be obtained by writing to Mr. H. I. Anderson, Business Manager, Biological Abstracts, University of Pennsylvania, Philadelphia 4, Pennsylvania.

The editors Dr. Emil Novak and Dr. Nicholson G. Eastman, of Baltimore, announce the publication of a new abstract periodical, *Obstetrical and Gynecological Survey*. It will cover the entire medical periodical literature, both foreign and domestic, and will appear bimonthly beginning in February 1946. Nine hundred pages per year will be published and the subscription price will be \$9.00. The Williams & Wilkins Company, of Baltimore, will be the publishers.

## OBITUARIES

### DR. WALTER BAUMGARTEN

Dr. Walter Baumgarten, F.A.C.P., of St. Louis, died at his summer home at Fish Creek, Wis., on August 23, 1945. A fire which destroyed his home caused his death.

His associates and his innumerable patients feel a great loss. Dr. Baumgarten for many years occupied a position of high importance in the field of Internal Medicine, and exerted a definite influence on the younger men who were associated with him in practice and at St. Luke's Hospital. He also made a deep impression by living up to a very high ideal of what the physician should be.

Born in St. Louis, October 31, 1873, it was natural for him to study Medicine, since his father was probably the outstanding Internist of his day in the Middle West, and one of the original members of the Association of American Physicians.

Walter Baumgarten obtained his college degree at Johns Hopkins University, and his medical degree at Washington University, where he was graduated in 1896. He was Assistant in Physiology in Harvard Medical School 1897-98, and Johns Hopkins University, 1902-03. He then became associated with Washington University School of Medicine, and maintained this connection until his death. He was deeply interested in the affairs of St. Luke's Hospital, and was at one time Director of the Department of Medicine. He was also Assistant Visiting Physician at Barnes Hospital.

He was a member of the St. Louis Medical Society, St. Louis Society of Internal Medicine, Missouri State Medical Association, and the American

Medical Association He was a Fellow of the American College of Physicians since 1920

RALPH A. KINSELLA, M D , F A C P ,  
Governor for Missouri

### DR JOHN GOOLD HARVEY

Dr John Goold Harvey, F A C P , died May 24, 1945, at the Veterans Administration Hospital, Dearborn, Michigan, of a cerebral hemorrhage. He had been an invalid for the last two or three years of his life.

Dr Harvey was born in Detroit in 1875. He attended Princeton University and graduated from the University of Michigan Medical School in 1902. He was at one time associated with the United States Public Health Service and served as a medical officer in the United States Navy during World War I. He was a member of the Wayne County Medical Society, the Michigan State Medical Society, American Medical Association, and Fellow of the American College of Physicians since 1920.

Dr Harvey spent most of his active years of practice in Detroit. He was highly respected by the members of his profession and enjoyed a nice practice with a very fine type of people. During the last few years of his practice he was physically handicapped and in spite of a splendid courage eventually had to retire. His passing is a deep loss to his many friends and patients.

P L LEDWIDGE, M D , F A C P ,  
Governor for Michigan

### DR FRIEDRICH ALEXANDER HECKER

Dr Friedrich Alexander Hecker, F A C P , for many years Pathologist at St Joseph's Hospital, Ottumwa, Iowa, died June 3, 1945, of coronary thrombosis.

Dr Hecker was born March 29, 1879. He attended Kemper Military School, Boonville, Missouri. He received a B S degree in 1908, an M A. degree in 1911, and an M D degree in 1913, all from the University of Kansas. He had previously received the degree of D D S in 1903 at the University of Pennsylvania. He served during the Spanish War, the Philippine Insurrection, and World War I. He was a Charter Member of the American Society of Clinical Pathologists, Diplomate of the American Board of Internal Medicine, and he had been a Fellow of the American College of Physicians since 1930. Dr. Hecker also was a member of the Wapello County Medical Society, Iowa State Medical Society, Iowa Clinical Society, the American Medical Association and the Society of American Bacteriologists.

Dr Hecker was an earnest, enthusiastic worker, an unusual technician,

and had a vigorous personality. He will be keenly missed by his many friends in the medical profession.

B F WOLVERTON, M D, F A C P,  
Governor for Iowa

### DR RAYMOND LUFT

The death of Dr Luft as the result of a coronary thrombosis while serving in the Navy has removed from the ranks of the profession of Rhode Island one of the most capable and promising of our young physicians.

He was born in Jersey City, New Jersey, in 1904, was graduated from Rhode Island State College in 1926, took up postgraduate studies at Brown University, and received his M D from McGill University in 1934. He served an internship at the Royal Victoria Hospital in Montreal and held a residency at the Massachusetts General Hospital.

Dr Luft began practice in West Warwick, where he held a part-time position in public health work, and later moved his office to Providence. He became a member of the Kent County and Rhode Island Medical Societies, and in 1939 was made an Associate of the American College of Physicians. At the start of his practice he joined the staff of the Rhode Island and Charles V Chapin Hospitals. He was particularly interested in diabetes and was active in the Diabetic Clinic at the Rhode Island Hospital. He was an internist of ability and his loss is keenly felt by his colleagues. This is particularly true of the writer, to whom Dr Luft was intimately known since his early student days.

ALEX M BURGESS, M D, F A C P,  
Governor for Rhode Island

### DR JOSEPH McFARLAND

Dr Joseph McFarland, F A C P, Philadelphia, died suddenly on September 22, 1945, at the age of 77. Born in Philadelphia, February 9, 1868, Dr McFarland graduated from the University of Pennsylvania in 1889. After further study in Europe, he returned to take up the teaching of Pathology. From 1896 until 1916 he was Professor of Pathology and Bacteriology at the Medico-Chirurgical College of Philadelphia. From 1910 to 1914 he also held the chair of Pathology in the Woman's Medical College of Pennsylvania. In 1916 he returned to the University of Pennsylvania as Professor of Pathology. He held the rank of Major in the first World War. Tuberculosis, contracted during his service in the Army, forced him to be relatively inactive for several years. However, by 1920 he was again actively teaching as Professor of General Pathology in the Thomas A Evans Institute of the University of Pennsylvania. He became Emeritus Professor of Pathology in the University of Pennsylvania in 1936 upon reaching the age of 68.

Dr McFarland wrote voluminously, being the author of at least four textbooks. Two of these, "The Pathogenic Bacteria and Protozoa" and "Textbook of Pathology," went through numerous editions.

Dr McFarland belonged to numerous societies and organizations. He had been a Fellow of the American College of Physicians since 1923.

His great zeal for teaching and his love of his profession are exemplified by his last years. Although "retired for age," in 1936, Dr McFarland resumed active teaching in 1940 as Professor of General Pathology in Temple University School of Dentistry. Not many months before his death he made an extensive lecture tour to a number of Latin American medical centers, an experience that gave him much satisfaction.

Active until the very end, he died as he would have wished, suddenly. His life was long and full. He will be held in affectionate memory by the many students who sat under him.

THOMAS M. McMILLAN, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### DR BENJAMIN A. SHEPARD

Dr Benjamin A. Shepard, F.A.C.P., died June 16, 1945, at his residence in Kalamazoo, Michigan.

Dr Shepard was born near Hillsdale, Michigan, July 13, 1879, and grew up in that community. He married Lola E. Hughes of Coldwater in 1900, just before entering the Detroit College of Medicine and Surgery. He was graduated from this institution, 1904, and practiced in Plainwell, Michigan, from 1904 to 1911. In that year he moved to Kalamazoo, Michigan, and became chief of staff of a small dispensary in 1912. Later he was the founder, owner and medical director of Pine Crest Sanatorium which was established in 1920. He was head of this fine institution for the treatment of tuberculosis, and especially interested in that field.

He was a past president of the Michigan State Tuberculosis Society, a member of the Board of Directors of the National Tuberculosis Association, and honorary president of the Kalamazoo Tuberculosis Association. He was a Fellow of the American College of Physicians, the American Medical Association, the American College of Chest Physicians, and past president and secretary of the Kalamazoo Academy of Medicine.

His passing is a distant loss to Kalamazoo and its surrounding territory.

P. L. LUDWIG, M.D., F.A.C.P.,  
Governor for Michigan

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## IDIOSYNCRATIC FEBRILE REACTIONS TO THIOURACIL: CLINICAL CHARACTERISTICS AND POSSIBLE PHARMACOLOGIC SIGNIFICANCE

By JANET W McARTHUR, M D, RULON W RAWSON, M D, and J H MEANS, M D, F A C P, *Boston, Massachusetts*

THIOURACIL has been employed in the preoperative preparation of 104 patients suffering from thyrotoxicosis at the Massachusetts General Hospital between April 1943 and April 1945. Toxic reactions (applying the term in the most inclusive sense) have occurred in 15 instances. In five cases, fever has been the most conspicuous feature of the reaction. Case reports of three † of these patients are presented, together with speculations as to the fundamental significance of the idiosyncratic response.

### CASE REPORTS

*Case 1* E H, a 40-year-old white married housewife, was admitted on April 8, 1944, complaining of weakness, easy fatigability, nervousness and a sense of oppression in the chest on exertion, of nine months' duration. One month prior to admission she noticed a swelling of her neck. She had lost 13 pounds despite a good appetite. Her family physician had treated her with iodine for four months prior to admission without conspicuous benefit. Physical examination disclosed a well-nourished woman with a flushed face. There was moderate bilateral exophthalmos with widened palpebral fissures, lid lag and impaired convergence. The thyroid gland was diffusely enlarged two and one-half times with thrill and bruit. Soft systolic murmurs were audible at the apex and pulmonic area. The red blood cell count was 4,310,000, hemoglobin 14.2 gm, and white blood cell count 5,100 with 68 per cent neutrophils, 20 per cent lymphocytes and 12 per cent monocytes. The urine was normal. Basal metabolic rates after bed rest were +28 and +27. The clinical diagnosis was classic exophthalmic goiter of moderate severity. Thiouracil was be-

\* Received for publication July 14, 1945.

From the Thyroid Clinic, Massachusetts General Hospital.

† One case is omitted because there was no opportunity to readminister the drug and confirm the clinical impression of drug fever. Another case is being reported separately because of the remarkable swelling of the parotid and submaxillary glands which was associated with the fever.

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gun in a dosage of 0.2 gm every eight hours. The patient remained afebrile until the seventh day of therapy, when the temperature rose to 103° F. The patient vomited and complained of slight soreness of the throat. The pharynx was moderately injected and the tonsillar and posterior cervical lymph nodes were enlarged and slightly tender. The white blood cell count was 11,000 and the differential 75 per cent neutrophils, 22 per cent lymphocytes and 3 per cent monocytes. The fever was ascribed to mild streptococcal pharyngitis and thiouracil continued. On the following day the patient was dizzy and nauseated. She vomited repeatedly. The rectal temperature rose to 105.6° F. Throat cultures taken the previous day showed a moderate growth of beta hemolytic streptococci, and two blood cultures were negative. Thiouracil was continued for another day. The next day the patient appeared moderately prostrated and continued to vomit. The temperature remained elevated. Positive physical findings included moderate pharyngeal injection, a questionable faint macular erythematous rash on the abdomen, and cervical lymphadenopathy. The liver edge was just palpable at the costal margin and the spleen could be felt one finger's breadth below the costal margin. The white blood cell count declined to 6,300 with 79 per cent neutrophils and 21 per cent lymphocytes. Thiouracil was withdrawn with prompt subsidence of

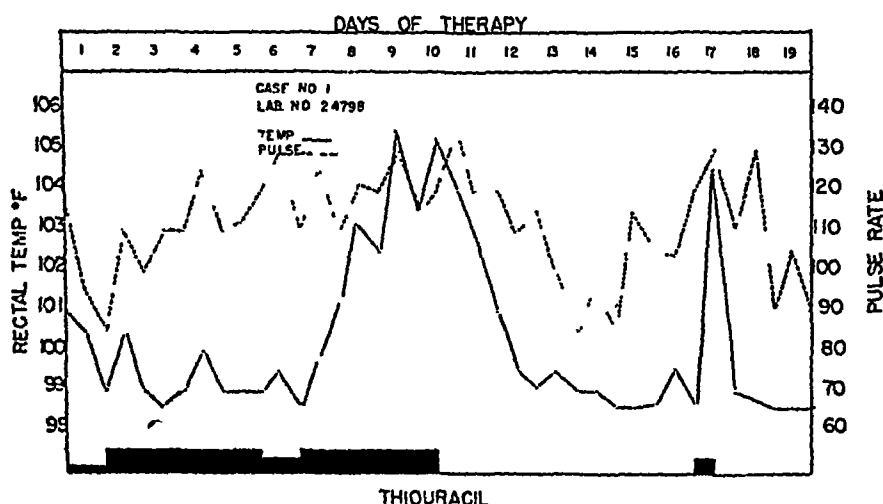


FIG 1 Clinical course of case 1 on thiouracil therapy

the fever. After four afebrile days two 0.2 gm doses of thiouracil were administered. Within a few hours the patient complained of malaise, anorexia and severe cramping pains in both legs. The rectal temperature rapidly rose to 104.4° F. The patient appeared acutely ill, with a reddish-purple flush on the face, chest and upper extremities. There was marked injection of the bulbar conjunctiva and moderate reddening of the throat. The white blood cell count rose to 18,300. Thiouracil was discontinued and surgical preparation completed with iodine. Subtotal thyroidectomy was performed without incident on May 22, 1944.

**Case 2.** M. F., a 65-year-old married colored housewife, was admitted on April 20, 1944, with a history of one year's enlargement of a lump which had been present in the neck for 40 years. During the three years prior to admission she had noted increased nervousness, mild heat intolerance and a weight loss of 35 pounds. On physical examination she was found to have an enlarged thyroid with a 3 by 3 cm hard nodule in the lower pole of the right lobe, a fine tremor, and eye signs consisting of lid retraction, lid lag and globe lag. The blood pressure was 180 mm Hg systolic and 90 mm diastolic and the heart moderately enlarged to the left. The red blood cell count was 4,050 (norm), hemoglobin 11.5 gm, and white blood cell count 9,300 with 39 per

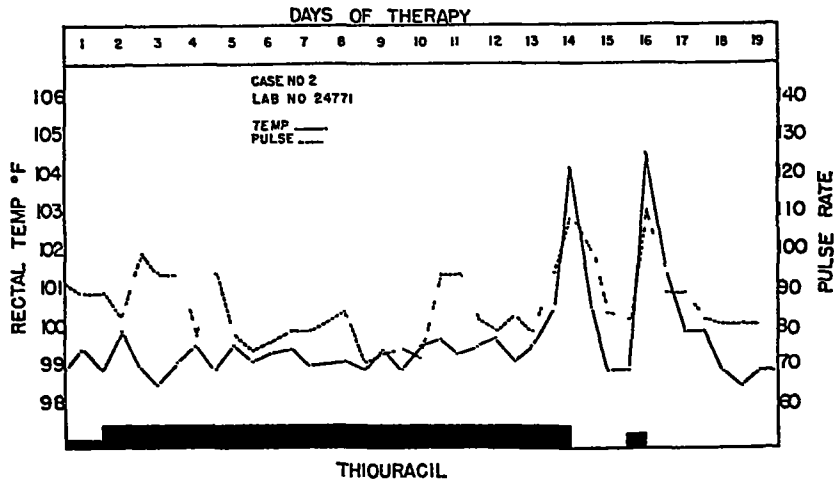


FIG 2 Clinical course of case 2 on thiouracil therapy

cent neutrophils, 38 per cent lymphocytes, 22 per cent monocytes and 1 per cent basophils. The urine was not remarkable. Clinical diagnoses of toxic nodular goiter and compensated hypertensive cardiovascular disease were made. Basal metabolic rates of +36 and +39 were obtained after rest in the hospital, whereupon thiouracil was begun in a dosage of 0.2 gm every eight hours. The course was uneventful until the fourteenth day of therapy, when the patient had a sudden shaking chill, after which the rectal temperature rose to  $104.4^{\circ}\text{F}$ . Physical examination was negative except for slight redness of the throat. The white blood cell count was 7,350 and a blood culture was negative. Thiouracil was immediately discontinued and within 36 hours the temperature was normal. Following two 0.2 gm doses of thiouracil the patient again developed severe shaking chills and a rectal temperature of  $105^{\circ}\text{F}$ . Prompt defervescence followed withdrawal of thiouracil. Preparation for operation was continued for five days with iodine alone and subtotal thyroidectomy performed uneventfully on May 12, 1944.

**Case 3** C M., a 68-year old ex-machinist, was admitted on May 19, 1944, with thyrotoxicosis of four years' duration which had proved refractory to conservative therapy with iodine and roentgen-ray. His chief complaints were easy fatigability,

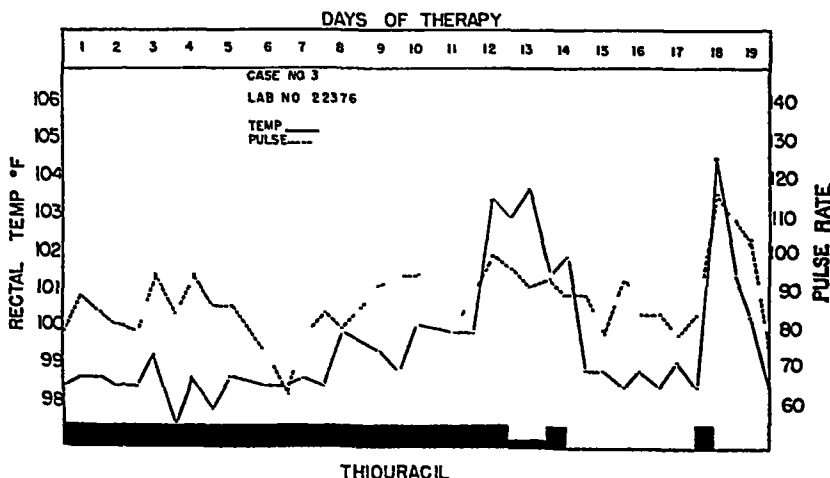


FIG 3 Clinical course of case 3 on thiouracil therapy

nervousness and slight burning of the eyes. Iodine was discontinued six weeks prior to admission to accelerate the response to thiouracil. On physical examination the patient appeared emaciated. The skin was moderately warm and there was a fine tremor of the fingers. The eyes displayed stare, lid lag and globe lag. The thyroid gland was just palpable. The tongue was red and fissured with smooth sore edges. A blowing systolic murmur was audible over the entire precordium, loudest to the left of the sternum. The red blood cell count was 3,890,000, hemoglobin 13 gm, and white blood cell count 5,950 with 45 per cent neutrophils, 40 per cent lymphocytes, 7 per cent monocytes and 8 per cent eosinophils. No abnormalities were noted in the urine. An electrocardiogram was suggestive of coronary heart disease. Clinical diagnoses of thyrotoxicosis, compensated arteriosclerotic heart disease and nicotinic acid and riboflavin deficiencies were made. After bed rest, basal metabolic rates of +34 and +31 were obtained and thiouracil started in a dosage of 0.2 gm every eight hours. The course was uneventful until the twelfth day of therapy when the temperature abruptly rose to 102° F. The patient complained of headache and a dull pain over the left anterior chest to the right of the lower sternum. The physical examination was negative except for moderate pharyngeal injection. The drug was continued for another 24 hours, during which the temperature continued elevated, ultimately rising to 103.8° F by rectum. The patient complained of crampy periumbilical pain. The white blood cell count was 5,700, a throat culture showed a moderate growth of beta hemolytic streptococci, and a chest roentgenogram was negative. The temperature promptly subsided after withdrawal of thiouracil. After an afebrile period of 72 hours, thiouracil was reëxhibited. Following the third 0.2 gm dose the rectal temperature rose to 104.6° F, and the patient complained of headache and malaise. Thiouracil therapy was abandoned and preparation for surgery completed with iodine. Subtotal thyroidectomy was performed on June 2, 1944, without untoward event.

## DISCUSSION

Drug fever has featured prominently among the toxic reactions to thiouracil reported by other investigators. Astwood<sup>1</sup> noted the development of fever in two of 30 cases, Williams and Clute<sup>2</sup> in two of 152 cases, Gabrilove and Kert<sup>3</sup> in two of nine cases, Gargill and Lesses<sup>4</sup> in two of 43 cases, and Bartels<sup>5</sup> in four of 119 cases, a grand total of 16 fevers among 457 treated patients, or an incidence of 3.5 per cent.

The clinical characteristics of the fevers in Astwood's and in Williams and Clute's series are not described. In one of the cases reported by Gabrilove and Kert, the fever developed on the tenth day of thiouracil therapy and was accompanied by generalized lymphadenopathy and a diffuse maculopapular erythematous eruption. The temperature was normal 24 hours after withdrawal of thiouracil and the drug was not given again. In the second case, the temperature rose abruptly on the eighth day of treatment and was accompanied by a purplish-red maculopapular eruption on the arms. Readministration of the drug resulted in abrupt rise in temperature to 105.4° F, and reappearance of the rash on the arms. Patch and scratch tests with thiouracil were negative. Gargill and Lesses' first patient experienced chills, fever, headache, and generalized aches and pains on the eighteenth day of thiouracil therapy. An abrupt recurrence and remission were observed.

when the drug was readministered and withdrawn. The second patient developed fever, choking sensations, nausea, vomiting, sweating and generalized aches and pains on the ninth day of thiouracil therapy. Reëxhibition of the drug provoked a sudden recurrence of these symptoms plus a non-productive cough, dyspnea, severe burning of the eyes with conjunctival injection, moderate splenomegaly and monocytosis. The four febrile reactions described by Bartels occurred within the first 10 days of treatment. The temperature reached 102-103° F, and was accompanied by generalized aches and pains. When thiouracil was discontinued it returned to normal and when thiouracil was resumed there was an immediate return of fever.

The sudden onset of fever after a relatively constant latent period of 10 days (range seven to 18 days), the explosive immediate reaction upon readministration of the drug, and the character of the accompanying symptoms suggest that thiouracil should be added to the roster of drugs which produce idiosyncratic reactions.

That drug idiosyncrasy, in many instances at least, comes into the same general category as anaphylaxis, has been established by the classical studies of Landsteiner.<sup>20</sup> He constructed immunologically active antigens artificially by conjugating pure chemicals with animal sera or with other proteins. The resultant antigen possesses a high degree of specificity which has been shown to depend upon the chemical radical and not upon the protein fraction of the conjugated antigen. Landsteiner was able to sensitize guinea pigs to arsphenamine so that anaphylactic shock was produced by the intravenous injection of the pure chemical uncombined with protein. Wedum<sup>21</sup> succeeded in sensitizing guinea pigs to azoproteins prepared from the sulfonamides.

The amazing heterogeneity of the list of drugs giving rise to idiosyncrasy (antipyrine,<sup>6</sup> arsphenamines,<sup>6</sup> barbiturates,<sup>6</sup> bismuth subsalicylate,<sup>7</sup> bromides,<sup>8</sup> cinchophen,<sup>9</sup> digitalis,<sup>10</sup> dilantin,<sup>11</sup> gold,<sup>12</sup> iodides,<sup>8</sup> mercurials,<sup>17</sup> nirvanol,<sup>13</sup> nitrates,<sup>8</sup> phenolphthalein,<sup>14</sup> quinine,<sup>15</sup> salicylates,<sup>6</sup> sulfonamides<sup>16</sup> and thiocyanates<sup>8</sup>) has been remarked upon by Coca. Indeed it is so impressive that it has led to the dismissal of allergic reactions as little more than spectacular, troublesome, and fortunately rare sporadic aberrations.

While reviewing the literature in an attempt to elucidate the nature of the reactions to thiouracil, the writers have been struck with the attention which has been lavished on the factors which may predispose an individual to develop an idiosyncratic reaction. Largely neglected have been the precise chemical factors which render an agent capable of inducing hypersensitivity. Such information as is available is summarized below, and an attempt is made to link the allergic and therapeutic actions on chemical grounds.

The fundamental dependence of the sensitizing capacity of a drug upon chemical structure is brilliantly illustrated by the hydantoin derivatives. Nirvanol (phenylethyl hydantoin) provokes an idiosyncratic response in 84 per cent<sup>13</sup> of the patients to whom it is administered whereas dilantin (sodium diphenyl hydantoinate) elicits an allergic reaction in only 5 per cent<sup>11</sup>

Hypersensitivity may be developed to the molecule as a whole, as is the case with antipyrine, or to certain radicals of the molecule. Doerr mentions cases of iodoform susceptibility in which the individual reacted also to bromoform, thus imputing the decisive rôle to the methyl radical. In a clinical study of quinine allergy, Dawson and Garbade<sup>15</sup> found the idiosyncrasy to extend to levorotatory alkaloids such as ethylhydriocuprine and cinchonidine but not to dextrorotatory isomers such as quinidine and cinchonine.

Propensity to induce idiosyncratic reactions is strong presumptive evidence of a drug's capacity to become bound to protein. In a number of instances, direct chemical evidence for this fact has been obtained. Thus, Davis<sup>22, 25, 26</sup> has demonstrated that the sulfonamide drugs become bound in varying degrees to serum albumin, leaving only a portion of the drug free to dialyze. In normal plasma the proportion of unacetylated drug which is bound to protein is as follows:

|               |     |
|---------------|-----|
| Sulfanilamide | 20% |
| Sulfapyridine | 40% |
| Sulfadiazine  | 55% |
| Sulfathiazole | 75% |

The plasma proteins, specifically the globulins, form compounds with the arspenamines both *in vitro* and *in vivo*<sup>29, 30</sup>. The cardiac glycosides bind serum albumin, as shown by Farah.<sup>27</sup> Data on the chemical properties of thiouracil are as yet meager. However, in developing a method for the quantitative determination of thiouracil in the blood, Williams<sup>34</sup> found that thiouracil is partially bound to protein, and can be liberated by tryptic digestion before assay.

That protein-binding capacity may have pharmacologic implications of considerable importance is suggested by Davis' discovery that the order of increasing tendency to be bound to plasma protein is identical with the order of increasing bacteriostatic effectiveness against *E. coli*. Since the bound drug apparently exerts no bacteriostatic action this result appears superficially paradoxical. However, there is considerable evidence for the belief that the antibacterial action of the sulfonamides is effected by competition for an enzyme associated with a metabolite essential for bacterial growth.<sup>27, 28</sup> Inasmuch as all enzymes are proteins, the tendency of a drug to become bound to plasma protein may reflect its tendency to bind enzyme protein.

The arspenamines are thought to exert their parasitocidal action by a somewhat similar mechanism after conversion into a partial oxidation product, arsenoxide. It is possible to protect trypanosomes and spirochetes from the lethal effects of arsenoxide by the addition of minimal amounts of glutathione and certain other sulfhydryl compounds. Since trypanosomes

\* Indeed the inhibition of bacterial growth by sulfonamides may be accounted for satisfactorily by assuming that the action is due to a reversible combination between the free form of the drug and the neutral form of the enzyme, and that the law of mass action is applicable.<sup>24</sup>

can be shown by the nitroprusside test to contain a sulfhydryl compound similar to glutathione, it is believed\* that arsenoxide combines with this sulfhydryl to oxidize it to a form incapable of performing an important rôle in the respiratory metabolism of the parasite which thereupon dies<sup>31</sup>

The prevention of thyroid hormone formation by the sulfonamides and thioureas may likewise prove to be due to an enzyme blockade mechanism. Dempsey<sup>36</sup> demonstrated the presence of peroxidase in the thyroid follicular cell by the benzidine test. The peroxidase reaction was easily inhibited by the addition of thiouracil to the reagents. It is of interest that some correlation exists between the protein-binding tendency of the sulfonamide drugs and their goitrogenic potency as ranked by Astwood<sup>37</sup>. He found that the goitrogenic potency of sulfonamides administered to normal rats increased in the following order: sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine.

The structural factors which condition the therapeutic action and the allergic reaction are doubtless of great complexity. Capacity of a drug to combine with protein *in vivo* does not necessarily mean that the resultant antigen is capable of arousing a major idiosyncratic response in the subject. Penicillin is perhaps an example of this type of drug. Chow and McKee<sup>38</sup> have recently demonstrated that human albumin will bind crystalline penicillin. Although urticaria develops in 2 to 5 per cent of patients treated, fever having the characteristics of true drug idiosyncrasy has not yet been reported. The febrile reactions that were seen in the early days of penicillin therapy seem to be attributable to impurities in the drug. Anderson<sup>39</sup> states that occasionally patients have been observed who maintain a low-grade fever after the clinical signs of infection have disappeared. In several of these cases, the temperature returned to normal when penicillin was withdrawn. Likewise, it is quite possible that some compounds combine with the enzyme but are not chemotherapeutically active. Thus, Davis and Wood<sup>26</sup> have found that metanilamide and various inactive substituted sulfonamides, as well as active sulfonamides, combine with plasma proteins.

The evidence summarized herein, while circumstantial, suggests that some of the chemical factors which determine the anaphylactic-like complications of chemotherapy may also determine the therapeutic effect. The heterogeneity of the drugs which give rise to idiosyncratic reactions should not blind us to their common characteristic which may possess fundamental pharmacologic importance, namely the capacity to bind proteins.

### CONCLUSIONS

1. Case reports of three patients with thyrotoxicosis who developed fever attributable to thiouracil therapy are presented. The clinical features

\* The fallacy implicit in deductions of modes of pharmacologic action from experiments involving their inhibition has been pointed out by Heubner in connection with these studies by Voegtlin. Heubner<sup>33</sup> shows that Voegtlin's conclusions are possibly (even probably) but not necessarily correct.

of these thiouracil reactions suggest that they are manifestations of true drug idiosyncrasy

2 Biologic factors predisposing an individual to develop an allergic response have been emphasized in the literature to the neglect of chemical factors rendering an agent capable of inducing hypersensitiveness

3 It is suggested that capacity to bind proteins is the common chemical factor which is responsible for the anaphylactic-like complications of chemotherapy as well as the therapeutic effect

### BIBLIOGRAPHY

- 1 ASTWOOD, E B. Medical treatment of hyperthyroidism, *Bull New England Med Center*, 1944, vi, 1
- 2 WILLIAMS, R H, and CLUTE, H M. Thiouracil for thyrotoxicosis, *Jr Am Med Assoc*, 1945, cxxviii, 65
- 3 GABRILOVE, J L, and KERT, M F. Sensitivity to thiouracil, *Jr Am Med Assoc*, 1944, cxxiv, 504
- 4 GARGILL, S L, and LESSFS, M F. Toxic reactions to thiouracil, *Jr Am Med Assoc*, 1945, cxxvii, 890
- 5 BARTEIS, E C. Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism, *Ann Int. Med*, 1945, xxii, 365
- 6 PETERS, E E. The syndrome of Milian's erythema of the ninth day, *Am Jr Syph*, 1941, xxv, 527
- 7 GRUND, J L. Erythema of the ninth day following bismuth therapy for syphilis, *Arch Dermat and Syph*, 1940, xli, 1076
- 8 BARKER, W H, and WOOD, W B, Jr. Severe febrile iodism during the treatment of hyperthyroidism, *Jr Am Med Assoc*, 1940, cxiv, 1029
- 9 SHORT, C L, and BAUFER, W. Cinchophen hypersensitiveness, *Ann Int Med*, 1933, vi, 1449
- 10 COHEN, R V, and BRODSKY, M L. Allergy to digitalis, *Jr Allergy*, 1940, xii, 69
- 11 MERPITT, H H, and PUTNAM, T J. Sodium diphenyl hydantoinate in the treatment of convulsive disorders, *Jr Am Med Assoc*, 1938, cxv, 1068
- 12 GOLDMAN, L, and CLARKE, G. Erythema of the ninth day syndrome, *Am Jr Syph*, 1939, xliii, 224
- 13 SCHICK, B, SOROTKA, H, and PECK, S. Chemical allergy and nirvanol sickness, *Am Jr Dis Child*, 1933, xlv, 1216
- 14 ABRAMOWITZ, E W. Reactions due to phenolphthalein, *Arch Dermat and Syph*, 1935, xxi, 777
- 15 DAWSON, W T, and GABBADE, F A. Idiosyncrasy to quinine, cinchonidine and ethylhydrocupreine, *Jr Am Med Assoc*, 1930, xciv, 704.
- 16 LONG, P H. The clinical use of sulfonamide compounds, *Nelson's New Loose-leaf Medicine*, N Y Vol I, Chap 4
- 17 VAUGHAN, W T. Practice of allergy, 1939, C V Mosby Company, St. Louis
- 18 WAINSTEIN, A, and SMITH, N. Sur la question de la symptomatologie de la pathogenie et de la pathologie des exanthemes precoces arsenobenzoliques "erythemes du neuvieme jour" de Milian, *Ann de dermat et syph*, 1937, viii, 215
- 19 LONGCORE, W T. Serum sickness and analogous reactions from certain drugs, particularly the sulfonamides, *Medicine*, 1943, xxii, 251
- 20 LANGE-RENN, K. Serological and allergic reactions with simple chemical compounds, *New England Jr Med*, 1936, cxxv, 1199
- 21 WELSH, A G. Immunological specificity of sulfonamide azoproteins, *Jr Infect Dis*, 1942, lxx, 173

- 22 DAVIS, B D Binding of sulfonamides by plasma proteins, *Science*, 1942, xcv, 78
- 23 FARAH, A On the combination of some cardio-active glycosides with serum proteins, *Jr Pharmacol and Exper Therap*, 1945, lxxxiii, 143
- 24 KLOTZ, I M The mode of action of sulfonamides, *Jr Am Chem Soc.*, 1944, lxvi, 459
- 25 DAVIS, B D The binding of sulfonamide drugs by plasma proteins A factor in determining the distribution of drugs in the body, *Jr Clin Invest*, 1943, xxii, 753
- 26 DAVIS, B D, and WOOD, W B, JR Studies on antibacterial action of sulfonamide drugs III Correlation of drug activity with binding to plasma proteins, *Proc. Soc Exper Biol and Med*, 1942, li, 283
- 27 FILDES, P A rational approach to research in chemotherapy, *Lancet*, 1940, xxi, 74
- 28 WOODS, D D The relation of p-aminobenzoic acid to the mechanism of the action of sulphanilamide, *Brit Jr Exper Path*, 1940, xxi, 74
- 29 YOUNG, W J. The fixation of salvarsan and neosalvarsan by the blood after intravenous injection, *Biochem Jr*, 1915, ix, 479
- 30 OLIVER, J, and DOUGLAS, E Biologic reactions of arsphenamine, *Arch Dermat. and Syph*, 1923, vii, 778
- 31 VOEGTLIN, C, DYER, H A, and LEONARD, C S On the mechanism of the action of arsenic upon protoplasm, *Pub Health Rep*, 1923, xxxviii (2), 1882
- 32 EAGLE, H The effect of sulphydryl compounds on the antispasmodic action of arsenic, bismuth and mercury compounds in vitro, *Jr Pharmacol and Exper Therap*, 1939, lxvi, 436
- 33 HEUBNER, W Chemische Reaktionen als Grundlage pharmakologischer Wirkungen, *Klin Wchnschr*, 1934, xiii (2), 1633
- 34 WILLIAMS, R H, JANDORF, B J, and KAY, G A Methods for the determination of thiouracil in tissues and body fluids, *Jr Lab and Clin Med*, 1944, xxix, 329
- 35 ASTWOOD, E B The chemical nature of compounds which inhibit the function of the thyroid gland, *Jr Pharmacol and Exper Therap*, 1943, lxxviii, 79
- 36 DEMPSEY, E W Fluorescent and histochemical reactions in the rat thyroid gland at different states of physiological activity, *Endocrinology*, 1944, xxxiv, 27
- 37 ASTWOOD, E B, SULLIVAN, J, BISSELL, A, and TYSLOWITZ, R Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat, *Endocrinology*, 1943, xxxii, 210
- 38 CHOW, B F, and MCKEE, C M Interaction between crystalline penicillin and human plasma proteins, *Science*, 1945, ci, 67
- 39 ANDERSON, D G The treatment of infections with penicillin, *New England Jr Med*, 1945, ccxxxii, 423



# MENINGOCOCCIC INFECTIONS WITH SPECIAL REFERENCE TO CERTAIN DIAGNOSTIC CONSIDERATIONS; AN ANALYSIS OF THIRTY-SEVEN CASES

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The comprehensive study of meningococcic meningitis and sepsis by Colonel Henry M Thomas, Jr,<sup>1</sup> concerns a total of 1,518 cases which occurred in the Fourth Service Command during the winter and spring of 1942-1943. The mortality rate of 88 per cent in the first 317 cases was lowered to 21 per cent in the last 761 cases. These rates are to be compared with the rate of 39 per cent in something less than 6,000 cases in the United States Army in 33 months during the First World War, and with reports (cited by Thomas) in which a mortality of "something over 50 per cent" is regarded as "very low."

The cases reported by Thomas, together with other large series now on record, make clear in the aggregate that sulfonamide therapy, if promptly and properly applied, can reduce the death rate of meningococcic infections to levels once believed impossible. The prompt application of therapy, however, rests upon prompt diagnosis, and prompt diagnosis is not always as simple as it seems. This is particularly true when the number of cases observed is small and when they occur sporadically or when their epidemic characteristics are slow to be realized.

Thirty-seven patients with meningococcic infection, in nine of whom meningeal localization did not occur, were observed at the Station Hospital, Camp Bowie, Texas, during the 13 month period ending January 24, 1944. Four of the nine patients with meningococcemia, of whom one died, and 23 of the 28 patients with meningitis, of whom one died, were treated during the period of national epidemic incidence, the other cases occurred sporadically.

The purpose of this communication is two-fold: to emphasize the clinical syndrome of meningococcic infection, particularly of the sporadic and the non-meningitic variety, and to illustrate by case reports the various atypical forms which this infection may assume. Additional data on the effectiveness of chemotherapy in this disease are presented incidentally.

## ANALYSIS OF CASES

The age range in this series was from 18 to 38 years, but only two patients were over 30 years of age, and 23 were under 22 years. There

<sup>1</sup> Received for publication April 2, 1945.

<sup>2</sup> From the Medical Service, Station Hospital, Camp Bowie, Texas.

were only two negroes in the series, one of whom had meningococcemia and the other meningococcic meningitis

It is striking, and in accord with other observations, that of the 28 patients with meningitis 24 had been in the Army less than four months, and 17 of these less than one month. All four of the patients with meningococcemia treated during the period of the epidemic had been in the Army less than three months, and three of these less than one month. The duration of service of the patients with sporadic disease varied from seven to 29 months and averaged 18.8 months.

It does not seem unreasonable that new and unhardened recruits should show a pronounced susceptibility to meningococcic infection, though it is somewhat paradoxical that measures taken to increase physical endurance and develop immunity should at first have a deleterious effect on both those factors. Fatigue due to rigorous training schedules lowers the soldier's resistance before it increases it, and inoculations against typhoid fever and tetanus, and vaccination against smallpox, affect the soldier's native immunity. Sampson,<sup>2</sup> for instance, who observed 78 cases of cerebrospinal fever among troops in a camp in Natal after inoculation with concentrated typhoid vaccine, suggests that although immunizing inoculation eventually encourages the production of specific antibodies, its immediate effect is to lower resistance to such diseases as cerebrospinal fever, particularly if fatigue is associated.

The four cases of meningococcemia observed during the epidemic season, in one of which the Waterhouse-Friedrichsen syndrome was apparent, were all acute, in contrast to the five cases observed sporadically, in all of which the disease was chronic.

The symptoms in the acute cases of meningococcemia included moderate to severe headache, chills, myalgia and arthralgia, and rapid temperature elevations, with an upper limit of 105.4° F. Vomiting, nuchal rigidity, and symptoms referable to the sensorium were not observed in any instance. Headache was a prominent feature in every case of chronic meningococcemia, and the temperature elevations ranged from 101° to 102.4° F. A rash was present in every case, whether acute or chronic.

Stiffness of the neck and a positive Kernig's sign were present in each of the 28 cases of meningitis, but headache, which varied from moderately severe to excruciating, was present in only 25 cases, and a rash in only 19 cases. Vomiting was present in 24 cases, and nausea without vomiting in another case. A shaking chill preceded the onset of meningeal involvement in 11 cases. Nine of the 28 patients had no symptoms referable to the sensorium. In the other 19 cases, mental impairment and drowsiness were observed in 16, coma in six, delirium in one, and an irrational state in one. The reflexes were sometimes exaggerated and sometimes absent. The temperature on admission to the hospital varied between 99.6° and 105.4° F, but most often was between 101° and 104° F.

The rash in the four acute cases of meningococcemia was predominantly pink and macular in two instances, and predominantly purpuric and petechial in one case each. It was first noticed on the chest, back and extremities, but eventually was generalized. In meningitis it varied from a faint, dull red, maculopapular rash to a widespread petechial eruption. Frequently the lesions were confluent. The rash was always more profuse and more pronounced than in the cases without meningeal localization.

In the acute cases of meningococcemia the white blood cell count ranged from 15,000 to 52,000 per cubic millimeter, and the polymorphonuclear percentage from 83 to 94. In the chronic meningococcemias the highest white blood cell count was 22,250 per cubic millimeter. In the cases of meningitis the leukocytosis ranged from 12,200 to 80,700 cells per cubic millimeter, and exceeded 30,000 cells in only nine cases. The polymorphonuclear leukocyte percentage was generally high, and ranged from 90 to 96 per cent in 15 cases.

In the cases of meningitis the average spinal fluid leukocyte count was 8,000 per cubic millimeter, the range being from 629 to 39,850, and the average polymorphonuclear percentage was almost 90 per cent. Meningococci were demonstrated in the smears of the spinal fluid in 14 cases, and by culture of the spinal fluid in nine cases. Seventeen positive blood cultures were obtained, two in cases of acute meningococcemia, four in cases of chronic meningococcemia, and 11 in cases of meningococcic meningitis. In the fatal case of meningococcemia the peripheral blood smear, as in certain other reported cases, showed many gram-negative diplococci which morphologically resembled Neisserian organisms.

#### DIAGNOSTIC CONSIDERATIONS

In the majority of cases in this series the diagnosis was made soon after the patient had been admitted to the hospital, but meningococcic infection was not the diagnosis on admission in a single instance. Three patients, including one with acute meningococcemia, were admitted without diagnosis, and in three other instances all of meningococcemia, the diagnosis on admission was fever of undetermined origin. The remaining diagnoses included nasopharyngitis in 16 cases, pneumonia in four, measles in three, influenza in two, and upper respiratory infection, bronchitis, otitis media, pyelitis, gastroenteritis, and schizophrenia in one case each. Such diagnostic errors are not unusual, particularly in meningococcemia. All but one of the 15 cases of this disease reported by Copeman<sup>2</sup> were incorrectly diagnosed on admission to the hospital, chiefly, the author notes, because the belief is still general that this is an unusual type of infection. Adams<sup>4</sup> also calls attention to the possibility of diagnostic errors because meningococcemia is overlooked, particularly when it occurs sporadically.

Part of the diagnostic confusion also arises because of too great reliance upon the laboratory. The blood culture is not necessarily positive when a

blood stream infection is present Only 17 positive cultures, as noted, were secured in these 37 cases, and the initial culture was not positive in a single one of the sporadic cases In one instance of meningococcemia seven successive blood cultures were negative, the organism being recovered on the eighth attempt, when the increased carbon dioxide tension technic was employed Again these circumstances are not unusual Copeman<sup>8</sup> eventually secured 14 positive cultures in his 15 cases of meningococcemia, but none was secured on the first attempt In one case of the series reported by Dickson and his associates<sup>9</sup> 22 samples of blood yielded only two positive cultures

As these facts suggest, the diagnosis of meningococcemia is likely to be overlooked if the possibility is not borne constantly in mind, particularly when meningococcic infection is not epidemic Obviously the diagnosis must be made before a positive blood culture is obtained, or indeed before any report on the blood culture is received, if one hopes to prevent the advent of meningitis

#### THERAPY AND RESULTS

Treatment was substantially the same in all of these cases, whether or not meningitis was present The basic plan was as follows As soon as the diagnosis was made and lumbar puncture and other diagnostic measures were carried out, an initial dose of 5 gm of sodium sulfadiazine was given by vein in 200 to 1,000 c c of physiologic salt solution, followed by the intravenous infusion of 1,000 c c of 5 per cent dextrose in physiologic salt solution

Intravenous therapy was continued in patients who were stuporous or who were nauseated and vomiting, 3 gm of sulfadiazine being given every eight hours Otherwise 1.5 gm of sulfadiazine was given by mouth eight hours after the last intravenous medication, and the same dosage was repeated every four hours for periods ranging from three to five days The dosage was then reduced to 1 gm every four hours, and later to 1 gm every six hours Treatment was always continued until the temperature had been normal from five to seven days The duration of treatment in this series averaged 9.5 days and the dosage averaged 71.5 gm In one instance of meningitis there was so much difficulty in entering the veins that sulfathiazole was given subcutaneously in a solution of 0.5 per cent; there was no local reaction, and the therapeutic effect was good The blood sulfadiazine level, which was determined daily in the first days of the illness and later on alternate days, ranged from 3.1 to 16 mg per cent It was 10.0 mg per cent or higher in 18 instances

The fluid intake was maintained at 4,000 c c daily, which produced a urinary output of 1,000 to 1,500 c c daily Intake and output were charted throughout the illness Intravenous fluids were administered whenever the oral intake was unsatisfactory for any reason Urinalysis and blood study

were carried out daily at first, and later on alternate days. Sodium amytal was used routinely by the intramuscular route to control restlessness.

Complications as the result of therapy developed in only six cases. One patient, who presented pleural effusion and pneumonia of the right lower lobe when he was first seen, developed a drug rash on the tenth day of treatment, and another patient a drug rash on the fourteenth day of treatment, both made uncomplicated recoveries when sulfadiazine was discontinued. One patient developed microscopic hematuria and one gross hematuria, both recovered uneventfully after withdrawal of the drug. One patient developed hematuria and anuria after he had received a total dosage of 64 gm of sodium sulfadiazine over a period of eight days. He recovered after ureteral catheterization and infusions of 10 per cent glucose solution. The sixth patient also developed gross hematuria but required no special treatment.

Two patients presented complications unrelated to therapy. The first developed arthritis of both wrists, which subsided without residue. The other developed pericarditis and suppurative arthritis of the right wrist and elbow, the left shoulder, and both knees. Purulent fluid was aspirated from the right elbow and both knees. Recovery was apparently complete, but two months later symptoms of neurocirculatory asthenia appeared, and the patient was discharged from the Army on this basis. The other surviving patients were returned to full duty in varying periods of time. Both deaths in the series occurred during the epidemic period.

#### CASE REPORTS

*Case 1.* A 19 year old negro, in service less than three weeks, became irrational and somewhat confused 48 hours after contracting a sore throat. Soon after being admitted to the hospital he presented a temperature of 105° F, his pulse became barely perceptible, and his blood pressure fell to 75 mm Hg systolic and 40 mm diastolic. He was in a stupor. The pupils were contracted and there was no reaction to light. The conjunctivae were injected. Numerous small petechiae were observed over the entire body, including the margins of the lower eyelids. A few were present on the hard palate. Knee jerks could not be elicited. The Babinski, Kernig and Brudzinski signs were negative.

Blood studies showed 52,000 white cells per cubic millimeter and 73 per cent of polymorphonuclear leukocytes. A smear showed many vacuolated disintegrated cells containing many gram-negative diplococci morphologically resembling Neisserian organisms. Blood culture taken under carbon dioxide tension showed gram-negative diplococci of Neisserian morphology, which were identified as meningococci by specific agglutination. The spinal fluid was clear and was not under increased pressure, the cell count was 5 per cubic millimeter, culture was sterile.

The patient died as he was being given an infusion containing sodium sulfathiazole at which time it was estimated that he had received only 1 gm. Death occurred 12 hours after admission to the hospital.

Autopsy revealed marked pulmonary edema and congestion of the lungs, liver and spleen, with petechial hemorrhages of the epicardium and gastrointestinal tract. The heart was dark blue and swollen, and cross section showed the coronary arteries filled with thrombi. Extensive hemorrhage was observed in the

*Comment* This patient had a fulminating septicemia with complicating Waterhouse-Friderichsen syndrome, which is characterized by sudden onset, overwhelming severity, cyanosis, shock, and a rapidly fatal outcome. The outstanding pathologic features were tissue congestion, edema, and petechiae, with massive bilateral adrenal hemorrhage. That the etiologic factor was an overwhelming meningococcemia is shown by the presence of the organisms even in the peripheral blood smear. Whether the state of shock was due to the septicemia or to the Waterhouse-Friderichsen syndrome it is not possible to say.

*Case 2* A 24 year old white soldier was hospitalized on a diagnosis of nasopharyngitis after developing a chill and fever of 104° F. Twenty-three hours later he presented a generalized purpuric and petechial eruption, petechiae being observed even on the conjunctivae. Shortly afterward he became drowsy and stuporous and exhibited signs of meningeal irritation. The spinal fluid was turbid, with a sugar content of 15 mg per cent, and a smear was positive for gram-negative diplococci. The patient did not respond to sodium sulfathiazole (25 gm intravenously) or concentrated antimeningococcic serum (15 cc intrathecally, 75 cc intravenously) and died in coma 84 hours after entering the hospital.

Autopsy revealed the following positive findings. Examination of the brain revealed a thin fibrinopurulent exudate over the vertex and lateral portion of the cerebral hemispheres, and, to a lesser degree, over the cerebellum. None was observed at the base of the brain. A thin fibrinous exudate was present over the pericardium and a small amount of purulent fluid was in the pericardial sac. The spleen was soft and slightly enlarged. A few petechiae were found on the jejunum and ileum, as well as in the lungs, which also showed edema and small scattered areas of bronchopneumonia. Microscopic section of the cerebral structures showed infiltration of the pia-arachnoid with polymorphonuclear leukocytes. It is to be noted that in this case the adrenal glands were both grossly and microscopically normal.

*Comment* Death in this case of fulminating meningitis with diffuse purpura and petechiae might have been avoided by prompt diagnosis and institution of treatment before the meninges were involved. Autopsy was remarkable only for the absence of exceptional findings other than those which would be observed in any instance of overwhelming sepsis.

*Case 3* A 19 year old white soldier was hospitalized for seven days with a temperature of 104° F, on a diagnosis of nasopharyngitis. After receiving 16 gm of sulfathiazole over a 60 hour period he was returned to duty in apparently good condition. Two days later he was readmitted to the hospital for malaise, headache, and a temperature of 101° F. Twelve hours later he developed nausea, vomiting, and nuchal rigidity. Petechiae were now present over the chest and abdomen. The white blood cell count was 80,700 per cubic millimeter, and culture showed meningococci. The spinal fluid was cloudy. The cell count was 6,900 per cubic millimeter and the sugar content was 34 mg per cent. The smear was positive for gram-negative diplococci and the culture was positive for meningococci.

Intravenous sulfadiazine therapy was begun at once, but six hours later the patient presented all the classic signs of shock, and cyanotic blotches covered the entire body. He was placed in an oxygen tent and was given 0.5 cc of adrenalin and 500 cc of plasma by vein. Clinical improvement was rapid. On the following day the urine was grossly bloody, but chemotherapy was continued cautiously and fluids were forced. The hematuria cleared up promptly and recovery was uneventful thereafter. The total dosage of sodium sulfadiazine was 58.5 gm over a 12 day period.

*Comment* This patient on his first admission evidently had an acute meningococcemia, which was unrecognized and, therefore, was inadequately treated. On his second admission he was extremely septic. The subsequent signs of circulatory col-

lapse were perhaps due to adrenal failure, which is not uncommon in severe infections. Whether or not this reasoning is valid, the patient responded promptly to the accepted treatment for this condition, and convalescence was smooth thereafter.

**Case 4** A 25 year old white soldier, in service for four months, awakened from sleep with chills, fever, severe headache, sore throat, malaise, and generalized aches in the neck, back and extremities. Vomiting soon followed. When admitted to the hospital he was apathetic and acutely ill. The temperature was 103° F and the pulse 108. The face was flushed. The pharynx was red and somewhat injected. The skin of the chest, abdomen, arms and thighs was covered by a dull red macular rash with numerous petechiae. Although a diagnosis of acute meningococcemia was made, therapy was withheld pending laboratory confirmation of the condition.

Seven hours after admission to the hospital, and following two episodes of projectile vomiting, the patient complained that his "head was bursting." He was rational and his temperature had fallen to 101° F, but he was pale and prostrated and was obviously much more seriously ill than when he was first seen. The entire body was now covered with a profuse, dull red, macular rash, which in many areas had petechial centers. There was now moderate nuchal resistance, and a suggestive Kernig's sign was observed, though the neck had been flaccid when he entered the hospital. Spinal puncture revealed turbid fluid under normal pressure. The cell count was 1,125 per cubic millimeter, the polymorphonuclear leukocyte percentage 91 per cent, and the total protein 178.6 gm per cent. The globulin was increased. Gram-negative intracellular diplococci were seen in the direct smear. The blood culture taken under carbon dioxide tension a few hours earlier, when no signs of meningeal irritation were present, was reported positive for meningococci. Recovery was uneventful following the administration of a total dosage of 80.5 gm of sodium sulfadiazine over a 16 day period.

**Comment** The clinical manifestations, the definite absence of signs of meningeal irritation, and the positive blood culture when the patient was first seen showed that at this time he had only an acute uncomplicated meningococcemia. Within seven hours this phase had passed into the phase of meningitis, which illustrates the speed with which meningeal involvement may come to pass in a patient with acute meningococcemia. It also illustrates the wisdom of instituting therapy before laboratory confirmation of the tentative diagnosis is obtained.

**Case 5** A 22 year old negro soldier had complained of headache and had appeared confused and sulky for several weeks. On several occasions he had fallen out of the ranks for no apparent reason, and shortly before entering the hospital, according to his battalion medical officer, he had developed "what is apparently a full blown schizophrenia."

The patient was uncooperative and resistive and was either unable or unwilling to supply much information about himself. The rectal temperature was 103.2° F. The neck was rigid and the abdomen was tense and resistant to pressure. Both the Kernig and Brudzinski signs were positive, and deep tendon reflexes were hyperactive. The white blood cell count was 38,850 per cubic millimeter and the polymorphonuclear leukocyte percentage was 90. The spinal fluid revealed 628 cells per cubic millimeter and a sugar content of 11 mg per cent.

The response to intravenous sulfadiazine therapy was dramatic and convalescence was uneventful. In all the patient received 515 gm of the drug over a nine day period.

**Comment** In this case mental symptoms, although secondary, over-shadowed the primary condition, so that the diagnosis of acute meningitis was at first overlooked. The following features, however, should always suggest the possibility of meningitis: (1) confusion, (2) hyperactive reflexes, (3) rigidity of the neck. In three cases reported by Weir and Vautier<sup>6</sup> the patients were so ill that they presented symptoms of confusion and

excitement, but all, like this patient, were later found to be suffering from acute meningitis. These authors emphasize that mental symptoms may be present for some time, as they were in this instance, before definite symptoms of meningeal irritation can be elicited. Adams,<sup>4</sup> who states that since entering the Army his "conception of meningococcic infection has been appreciably altered," points out that in some instances of acute meningitis an acute psychosis, most often of the maniacal type, may be the first and only symptom. He observed two such patients who had been admitted to psychiatric wards, and is of our opinion that in any case of sudden febrile psychosis without obvious cause meningitis should be suspected, even in the absence of temperature elevation.

*Case 6* A 32 year old white soldier developed chills, fever, severe headache, generalized aches and pains, and backache, which increased in severity over a 24 hour period. When he was first seen the face was flushed and there was a discrete, dull red, macular rash over the chest, back and abdomen, the macules of which faded on pressure. The pharynx was injected and moderately red. The white blood cell count was 17,850 per cubic millimeter and the polymorphonuclear leukocyte percentage was 85. A smear obtained by aspiration of one of the macules revealed no organisms. Culture of material from the throat was negative on three occasions, and blood culture was also negative.

The patient's symptoms disappeared shortly after he entered the hospital, his rash receded, and for three days he was afebrile, although the pharynx remained moderately red and injected. On the fourth day he again complained of headache, backache, and generalized aches and pains. The temperature rose to 103° F, and he was confused and slightly delirious. The macular rash reappeared on the abdomen, back and extremities. Six hours later the aches and pains and the backache became more severe, and he complained of chilliness. The macular rash extended to involve the chest, arms, and dorsum of both feet.

A blood culture taken at this time was later reported positive. Without waiting for laboratory confirmation, however, chemotherapy was instituted by the oral route a total of 53 gm of sodium sulfadiazine being given over a 10 day period. Within 24 hours after the drug had been begun clinical symptoms disappeared, the rash began to fade, and there were no further temperature elevations.

*Comment.* This case is another illustration of the fallacy of relying upon a negative blood culture to exclude the possibility of chronic meningococcemia. It also illustrates the fact that when diagnosis is still somewhat doubtful the disappearance of a petechial or macular rash in response to chemotherapy is a useful diagnostic measure.

*Case 7* A 25 year old white nurse was seen in consultation by one of us (A C O) on the twenty-first day of her illness. She had been awakened from sleep by severe lumbar backache, which had been followed successively by chilly sensations, pain in both inguinal regions radiating toward the pubis, and severe headache involving the entire occiput. When she was hospitalized at the end of 24 hours her headache was much worse, and attempts to flex the neck caused soreness and pain. At this time the temperature was 103.6° F. Physical examination was negative except for a macular rash over the whole body and slight tenderness in both inguinal regions. The white blood cell count was 22,250 per cubic millimeter, and the polymorphonuclear leukocyte percentage was 91. Blood smears were repeatedly negative for malaria, and smears from the cervix, seven blood cultures, and roentgenologic examination of the chest, sinuses, gall-bladder and colon were also negative.

Various diagnoses were considered at various times in the first 21 days of hospitalization. The first suggestion was meningismus. Chills and temperature elevations between 101° and 105° F which occurred every two to three days, suggested malaria. Persistent low backache, persistent low abdominal pain, dull pain in the



joints of the left hand and wrist, and the irregular macular rash were points in favor of the diagnosis of pelvic inflammation, diverticulitis of the colon, and rheumatic fever, respectively

When the patient was first seen in consultation she had just had a chill and her temperature was  $103^{\circ}\text{F}$ , but the only other complaint was a moderately severe headache. Physical examination revealed nothing except several maculopapular spots scattered over the extremities, dull red, 0.5 cm in diameter, disappearing on pressure, and without petechiae.

A diagnosis of chronic meningococcemia was made on the basis of the history and physical findings. Blood cultures on special media taken under carbon dioxide tension were twice reported positive for meningococci. The patient was given a total of 34 gm of sodium sulfadiazine over a five day period and an average blood sulfadiazine level of 12.4 mg per cent was thus achieved. The response to therapy was dramatic, symptoms disappeared promptly, and there were no further temperature elevations. The patient was discharged from the hospital 13 days after the administration of sulfadiazine was begun.

*Comment.* This case illustrates the bizarre picture and the mimicry of various diseases which meningococcal septicemia may present. The typical symptoms and signs of meningococcal disease, which usually make the diagnosis possible when the meninges become involved, are lacking in the septicemic stage, and both diagnosis and specific therapy may therefore be delayed, as they were in this case. A similar but less severe instance of meningococcal septicemia with intermittent fever suggestive of malaria has been reported by Kilham.<sup>7</sup>

*Case 8.* A 24 year old white soldier was admitted to the hospital three weeks after he began to experience aches and pains in the knees and ankles, which later involved the entire body and were associated with a sensation of stiffness. He also suffered from malaise, severe headaches, and afternoon rises of temperature to  $103^{\circ}\text{F}$ . A blotchy red eruption over both thighs and the dorsum of both feet appeared with the temperature elevations and blanched with their disappearance.

On admission to the hospital the patient did not seem acutely ill. The temperature was  $101.6^{\circ}\text{F}$ . The pharynx was moderately injected and there was a deep-seated follicular exudate over the upper pole of the right tonsil. Many reddish pink macules, varying in diameter from 0.5 to 1 cm, were scattered over both thighs. Some faded completely on pressure but a few exhibited central petechiae. No physical findings were elicited to explain the arthralgia, which was most marked in both ankles and the right knee. All reflexes were hyperactive. The Kernig, Brudzinski and Babinski signs were negative. The white blood cell count was 14,100 per cubic millimeter, and the polymorphonuclear leukocyte percentage was 85 per cent. The tentative diagnoses were rheumatic fever, erythema nodosum, periarticular rheumatism, and meningococcemia.

For the first days of hospitalization the patient continued to complain of pain in

main obscure and untreated for several months if the patient does not consult a physician promptly Campbell<sup>8</sup> reports four cases in which the average interval between onset and hospitalization was 28 days In another sporadic case in our own series the patient apparently had a chronic meningococcemia which had gone unrecognized for more than two months

*Case 9* A 38-year old white soldier, in service for 12 months, woke from sleep "freezing" and with a severe headache A shaking chill was followed by a rise in temperature and two other chills Malaise, myalgia and arthralgia had also developed before he was hospitalized At this time the temperature was 102.4° F and the pulse 104 The pharynx was red and injected A discrete, dull red, macular rash was present over the back, upper extremities, and dorsum of both feet The white blood cell count was 19,250 per cubic millimeter, and the polymorphonuclear leukocyte percentage 90 per cent Roentgenologic examination of the chest was negative, as was the blood culture

Sulfadiazine therapy was instituted immediately, on a diagnosis of early meningococcic septicemia, and a total of 44 gm was given over an eight day period The temperature declined by lysis and was permanently normal after the third day, by which time all clinical symptoms had also disappeared

*Comment* After the patient's recovery it was learned that two weeks before the onset of his illness he had visited his home, and that the day after he had been hospitalized he had received word that his three year old child had died of cerebrospinal meningitis Although no positive blood culture was ever secured, the history of direct contact, the characteristic clinical manifestations, and the dramatic response to therapy favor this being an instance of acute meningococcic septicemia

### SUMMARY AND CONCLUSIONS

Thirty-seven cases of meningococcic infection, nine of which were instances of meningococcemia without meningeal involvement, are briefly analyzed, and special diagnostic difficulties are illustrated by case reports

As this series makes clear, the successful therapy of meningococcic infections depends upon two considerations

- 1 Prompt and adequate chemotherapeutic measures, which imply the initial administration of the sulfa drugs by the parenteral route if necessary The institution of chemotherapy, however, depends upon

- 2 Early recognition of the disease, preferably before meningeal involvement occurs Such recognition is achieved only by the constant recollection that meningococcic infection can mimic any acute infectious process, can present superficially a picture of mental illness, and is frequently introduced by nasopharyngitis, headache and backache, all of which are symptoms of many other much less serious diseases

### BIBLIOGRAPHY

- 1 THOMAS, H M, JR Meningococcic meningitis and septicemia Report of outbreak in Fourth Service Command during Winter and Spring of 1942-1943, Jr Am Med Assoc, 1943, CXXXIII, 264-272
- 2 SAMPSON, B F Resistance of the new recruit (Letters to the Editor), Lancet, 1941, I, 772-773
- 3 COFFMAN, W S C Meningococcal septicemia Brit Med Jr, 1942, I, 760-761

- 4 ADAMS, F D Some clinical aspects of meningococcic infection, *Ann Int Med*, 1944, xx, 33-40
- 5 DICKSON, R C, MCKINNON, N E, MAGNER, D, and MCGILLIVRAY, N B Meningococcal infection, report of 50 cases, 40 treated with serum and 10 treated with serum and sulfanilamide, *Lancet*, 1941, ii, 631-634
- 6 WEIR T W H, and VAULTIER, C K Mental symptoms in cerebrospinal meningitis, *Brit Med Jr*, 1942, i, 179-181
- 7 KILHAM, L Meningococcal septicaemia with a malarial type of fever, *Brit Med Jr*, 1942, ii, 696
- 8 CAMPBELL, E P Meningococcal meningitis, *Ann Int Med*, 1942, xvi, 694-700



a few hours after splenectomy at the age of 52. Thromboses involving the portal system, extremities, and nervous system are common complications<sup>1, 4, 5, 6</sup>

The hemolytic character of the anemia is demonstrated by the following findings: bilirubinemia, absence of bile in the urine, and increased urine urobilinogen, together with signs of greatly increased bone marrow activity as evidenced by polychromatophilia, reticulocytosis, and the finding of hyperplasia of the erythrocytic marrow elements on direct examination. The red cells do not exhibit spherocytosis, and fragility to hypotonic saline solutions is within normal limits. The hemoglobinuria, which is secondary to hemoglobinemia, is characterized by the appearance of oxyhemoglobin and methemoglobin in the urine. Hemosiderinuria is a constant finding.

Leukopenia due primarily to neutropenia and a tendency to thrombocytopenia is observed in most cases. Both return to normal levels if splenectomy is performed.

#### CASE REPORTS

*Case 1.* G. R., aged 20, American born of Mexican-Spanish descent, was observed in naval hospitals from January 14, 1944 until December 29, 1944.

On admission to the sick list he complained of general malaise, asthenia, fever and sore throat of four days' duration and of dark urine for one day. There was no family history of anemia, hemoglobinuria, or jaundice.

The positive physical findings were temperature of 99.2° F., pallor, icteric sclerae, slight yellowish tinting of the skin, and moderate nasal-pharyngeal injection.

Laboratory findings summarized from his 12 month hospitalization were as follows:

Red blood cells 2,870,000, hemoglobin 9 gm., 58 per cent, white blood cells polymorphonuclear leukocytes 47 per cent, lymphocytes 50 per cent, monocytes 2 per cent, reticulocytes 7 per cent, red cell mean volume 115 cu.  $\mu$ , mean corpuscular hemoglobin concentration 26.5 per cent, mean corpuscular hemoglobin 31 micromicrograms, mean red cell diameter 8 microns, corpuscular thickness 2 microns, platelet count 200,000. The red cells in preparations tended to fold and curl around the periphery but target cells were observed. No spherocytosis or sickling was found. Stained smears showed polychromatophilia and anisocytosis. Erythrocyte hemolysis began at 0.36 per cent and is complete at 0.24 per cent NaCl compared with 0.52 per cent and 0.46 per cent respectively for the control. The Ham erythrocyte hemolysis tests are summarized in table 2. Spherocytosis was not found even in the tubes

agglutinins were present in the patient's serum to a dilution of 1:64 with his own cells and 1:8 with Group O cells of a normal individual. Autohemolysins were not demonstrable.

*Urine* revealed hemosiderin, free hemoglobin and urobilinogen. The first morning urine specimen tended to be darker than those voided during the remainder of the day and showed increased amounts of hemoglobin.

*Röntgenograms* of the chest, long bones, skull, intravenous pyelograms, and cholecystograms were within normal limits.

Liver function tests showed a positive cephalin flocculation test on two occasions. Hippuric acid tests were within normal limits. Urea clearance tests revealed normal renal function.

*Clinical Course* During the 12 month period of observation the patient had two paroxysms of hemoglobinuria lasting 24 to 36 hours associated with febrile upper respiratory infections. Transient hemoglobinuria occurred spontaneously on numerous occasions and the first morning urine specimen tended to be darker than others. The icterus index fluctuated from 15-25, the white blood cell count from 2,100 to 6,000, the lymphocyte percentage from 50-74 per cent, and the reticulocytes from 5-15 per cent.

Treatment, consisting of iron preparations orally and liver extract intramuscularly, was ineffective.

He felt surprisingly well except during the upper respiratory infections with associated hemoglobinuria, and was able to carry out a work detail throughout his period of hospitalization.

*Case 2* A. P. H., Pvt U. S. M. C., aged 30, was admitted to the sick list February 28, 1943 at Guadalcanal, Solomon Islands, because of an indolent superficial ulcer of the left leg of three months' duration and his first attack of malaria, type undetermined. Malaria subsided on routine atabrine therapy, and he was transferred to a rear area hospital for treatment of the chronic leg ulcer.

His past history was essentially negative except for three transient attacks of dark red urine occurring in December 1941, February 1942 and May 1942, before enlistment, and five attacks since enlistment. Physical examination was negative except for an indolent granulating leg ulcer. On March 25, 1943 wine red urine and slight icterus were noted. Malaria smear was positive for *Plasmodium vivax*. The hemoglobinuria cleared up in two days and malaria smears became negative on a régime of quinine, atabrine and plasmochin. On April 10, 1943 moderate fever developed. Smears for malaria and urinalysis were negative. Two days later, after temperature had subsided, the spleen was palpable and he passed wine red urine which gave a strongly positive benzidine test but revealed no red blood cells on microscopy. Fever, chills and hemoglobinuria appeared again May 2, 1943. Blood smears were positive for malaria. Symptoms, hemoglobinuria and evidence of malaria subsided promptly on a régime of five transfusions and atabrine.

He was received at this hospital July 2, 1943, feeling well except for the indolent left pretibial ulcer which healed quickly with the application of an Unna's paste boot. Fever began August 23 and moderate icterus was apparent. Two days later he had chills, fever to 104° F and dark wine red urine. Blood serum was reddish brown. The spleen was palpable. Smears for malaria showed infection with *Plasmodium vivax*. Chills, fever and hemoglobinuria subsided in seven days on a régime of bed rest, alkalization and seven transfusions of 500 cc each. Thin smear for malaria was negative August 30, although no antimalarial drugs had been given. Quinine started September 4 did not precipitate further hemoglobinuria.

On December 11, 1943, while up and active, he had abrupt onset of semiconsciousness and a right hemiplegia from which he slowly improved to about 60 per cent recovery of function. He had no further evidence of malaria following the severe

attack associated with hemoglobinuria in August. Transient hemoglobinuria, without associated fever or malaria, recurred on three occasions before he was discharged from the service July 28, 1944.

During the one year period of observation in this hospital, the red blood cell count fluctuated from 2,550,000 to 3,680,000, rising briefly to 4,229,000 after transfusions, the white cell count fluctuated from 3,250 to 7,000, hemoglobin from 7.5 to 11 gm, polymorphonuclear leukocytes from 68 per cent to 38 per cent, lymphocytes from 62 per cent to 30 per cent, icterus index from 15 to 40, and reticulocytes from 1 per cent to 12 per cent. Red blood cell fragility to hypotonic saline solutions was within normal limits. Blood Kahn reaction was negative. Total serum protein was 6.22 gm per cent. Blood non-protein nitrogen was 27 mg per cent. The urine was positive for hemoglobin and urobilinogen on numerous occasions. Liver extract intramuscularly and liver and iron orally were ineffectual in relieving the anemia.

He was first seen by the author when he reentered this hospital October 25, 1944. No malarial relapse or gross hemoglobinuria had occurred since July 28, 1944. The essential physical findings were scleral icterus, pallor, and residuals of the right hemiplegia. The spleen was not palpable. Laboratory findings were as follows: Red blood cells 3,180,000, hemoglobin 9 gm, white blood cells 5,300, polymorphonuclear leukocytes 50 per cent, lymphocytes 45 per cent, red cell polychromatophilia and anisocytosis, reticulocytes 6 per cent; red cell mean corpuscular volume 113 cu  $\mu$ , mean corpuscular hemoglobin 29, mean corpuscular hemoglobin concentration 29, and normal red cell fragility to hypotonic saline. No spherocytes or sickling of erythrocytes was observed. Gastric analysis showed free acid after histamine. Urine was positive for hemosiderin, hemoglobin and urobilinogen. The Ham erythrocyte hemolysis tests were positive as tabulated in table 2.

Treatment, consisting of iron preparations orally and liver extract intramuscularly, was ineffectual. Transfusions precipitated no untoward reactions and caused transient improvement in his anemia but were of no lasting benefit.

## DISCUSSION

malaria itself also contributed to the anemia so that the extent of erythrocyte destruction due solely to hemolysis can not be estimated

Typhoid vaccine intravenously and a febrile reaction following intramuscular medication induced hemoglobinuria in a patient reported by Scott, Robb-Smith and Scowen<sup>6</sup> However, febrile infections and reactions do not invariably induce paroxysms One of Hamberger and Bernstein's<sup>5</sup> cases had repeated febrile episodes in association with *B coli* pyelitis but hemoglobinuria occurred on only one occasion Paroxysms have also been observed in association with anesthesia,<sup>4</sup> the menstrual period,<sup>5</sup> after ingestion of acid salts such as ammonium chloride,<sup>4</sup> and after abruptly stopping alkalis given orally<sup>4</sup> Physical exertion does not accelerate hemolysis<sup>8</sup>

*Catabolism of Extracorporeal Hemoglobin and the Significance of Hemosiderinuria* Hemoglobinemia, as observed in both of our cases, is a

TABLE I

The Pertinent Laboratory Data during an Acute Hemolytic Crisis Precipitated by a Relapse of Benign Tertian Malaria in Case 2

| Date    | Red Blood Count | Hemoglobin Gm | White Blood Count | Polys % | Lymph % | Malaria Smear | Gross Hemoglobinuria | Transfusions Citrated Blood |
|---------|-----------------|---------------|-------------------|---------|---------|---------------|----------------------|-----------------------------|
| 8/23/44 | 3,220,000       | 10.5          | 7,750             | 63      | 36      |               | Negative             |                             |
| 8/24/44 | 2,390,000       | 7.5           | 3,900             | 60      | 37      | Positive      | ++++                 |                             |
| 8/26/44 | 2,900,000       | 9             | 5,900             | 57      | 40      | Positive      | ++++                 | 1,000 c c                   |
| 8/28/44 |                 |               |                   |         |         |               | ++++                 | 1,000 c c                   |
| 8/30/44 | 2,780,000       | 9             | 4,500             | 38      | 56      | Negative      | Negative             |                             |
| 8/31/44 |                 |               |                   |         |         |               | Negative             | 1,000 c c                   |
| 9/ 1/44 | 3,340,000       | 10.5          | 3,800             | 42      | 57      | Negative      | Negative             |                             |

constant finding Fairley<sup>9</sup> found the extracorporeal hemoglobin is in the form of oxyhemoglobin and methemalbumin The urinary pigments consist of hemosiderin, oxyhemoglobin in alkaline urine, and oxyhemoglobin and methemoglobin in acid urine

Extracorporeal circulating hemoglobin is disposed of in three ways by absorption into the reticuloendothelial system, by intravascular catabolism into methemalbumin, and by renal excretion<sup>9, 10</sup> After small intravenous injections, the free plasma hemoglobin is catabolized entirely by the reticuloendothelial system<sup>10</sup> With injections sufficient to raise the plasma hemoglobin level in adults with normal kidneys to above 100–135 mg per cent, hemoglobin also appears in the urine<sup>10, 11</sup> In more massive hemoglobinemia, such as transfusion reactions and blackwater fever, intravascular catabolism to methemalbumin likewise occurs<sup>9, 10</sup> Methemalbumin is not excreted in the urine but is catabolized by the liver<sup>10</sup> In moderate hemoglobinemia as little as 10 per cent of the extracorporeal hemoglobin appears in the



urine<sup>3, 9, 10</sup> As the hemoglobinemia increases the percentage of recovery in the urine rises to as high as 30–40 per cent<sup>12</sup>

The renal excretion of hemoglobin is dependent on the balance between filtration through the glomerular membrane and tubular reabsorption<sup>13</sup> The threshold is relatively high at first but, with daily intravenous hemoglobin injections, it decreases as much as 46 per cent<sup>17</sup> This decrease coincides with stuffing of the convoluted tubular epithelium with hemosiderin originating from hemoglobin reabsorbed from the glomerular filtrate<sup>13, 14</sup> That the hemosiderin is available for utilization in rebuilding hemoglobin is indicated by the fact that the rate of disappearance from the tubular epithelium is accelerated in anemia<sup>15</sup> It is a reasonable assumption that in constant stuffing of the convoluted tubular epithelium with hemosiderin, as a result of chronic hemoglobinemia above the minimal renal threshold level, the hemosiderin is likewise disposed of by excretion into the urine

Clinical observations support this thesis. Hemosiderinuria is not observed in acute intravascular hemolytic states such as favism, blackwater fever, transfusion reactions, a case of idiopathic acute massive hemoglobinuria reported by Altshule and Gilligan,<sup>8</sup> or after single intravenous injections of hemoglobin.<sup>11</sup> It is invariably found in chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria in which chronic hemoglobinemia, hemoglobinuria and stuffing of the convoluted tubular epithelium with hemosiderin occurs Hemosiderinuria is not to be considered as occurring solely in chronic hemolytic anemia with paroxysmal hemoglobinuria but rather as indicating the existence of prolonged hemoglobinemia above what Lichty, Havill and Whipple<sup>18</sup> have termed the "minimal renal threshold"

*Pathologic Physiology* Ham<sup>4</sup> interpreted the increased hemolysis occurring during sleep as indicating the erythrocytes were unusually susceptible to slight decreases in pH He substantiated his deductions by demonstrating that patients' red cells hemolyzed in acidified control and patients' serum while control cells showed no hemolysis Hemolysis did not occur if the serum was previously heated to 56° for one hour He concluded that in this disease an abnormality exists in the patient's erythrocytes which makes them reactive to a thermolabile factor occurring normally in serum and that the hemolytic reaction is accelerated by any decrease in pH

The erythrocyte hemolysis reactions of our two patients to Ham's tests are recorded in table 2 and conform with his findings

As noted in table 2 spherocytosis does not occur even in the tubes exhibiting hemolysis Spherocytic erythrocytes were likewise absent from the peripheral blood in both of our patients This is in direct contrast to most other types of hemolytic anemia and acute hemoglobinurias in which spherocytosis represents an actual phase in the process of erythrocyte disintegration<sup>19</sup> and indicates a different hemolyzing mechanism is involved

No abnormal serum hemolysins were found in case 1 which conforms with the findings of other observers

The chronic hemoglobinemia and lack of benefit from splenectomy indicates that hemolysis occurs intravascularly<sup>16</sup> instead of in the reticulo-endothelial system

*Treatment* No satisfactory treatment has been devised Splenectomy has produced no permanent benefit<sup>4, 5, 6</sup> and has been followed by death in some instances<sup>6</sup> Two splenectomized cases of Ham's<sup>4</sup> no longer showed leukopenia or the characteristic increase in red cell hemolysis during sleep but otherwise the clinical course was unaltered Alkalinization is ineffectual and is frequently followed by hemoglobinuria<sup>4</sup> Concurrent infections should be treated carefully because of their tendency to precipitate hemolytic reactions Transfusions were used repeatedly to combat the anemia in

TABLE II

Erythrocyte Reactions of Cases 1 and 2 and the Control under Varied Conditions of the Ham Hemolysis Tests

| Case |   | Patient's<br>Cells<br>Patient's<br>Serum | Control<br>Cells<br>Patient's<br>Serum | Patient's<br>Cells<br>Control<br>Serum | Control<br>Cells<br>Patient's<br>Serum | Erythrocyte<br>Spherocytosis |
|------|---|--|--|--|--|------------------------------|
| I    | Untreated Serum   | 0  | 0                                      | 0                                      | 0                                      | 0                            |
|      | Serum acidified with 0.05 cc<br>1/3 N HCl                                 | ++++                                     | 0                                      | ++++                                   | 0                                      | 0                            |
|      | Serum heated to 56° 1 hour,<br>0.05 cc 1/3 N HCl                          | 0  | 0                                      | 0                                      | 0                                      | 0                            |
|      | Serum heated to 56° 1 hour,<br>0.05 cc 1/3 N HCl<br>Guinea Pig Complement | 0  | 0                                      | 0                                      | 0                                      | 0                            |
| II   | Untreated Serum   | 0  | 0                                      | 0                                      | 0                                      | 0                            |
|      | Serum acidified with 0.05<br>cc 1/3 N HCl                                 | ++++                                     | 0                                      | ++++                                   | 0                                      | 0                            |
|      | Serum heated to 56° 1 hour,<br>0.05 cc 1/3 N HCl                          | 0  | 0                                      | 0                                      | 0                                      | 0                            |

case 2 without any untoward reactions Others<sup>4, 5, 6, 17</sup> have encountered severe reactions and are of the opinion that transfusions should be avoided even though hemolytic activity may be diminished as long as six weeks after a transfusion reaction<sup>4, 17</sup>

### DIFFERENTIAL DIAGNOSIS

Congenital hemolytic icterus is readily differentiated by the familial history of anemia and jaundice, spherocytic erythrocytes, increased erythrocyte fragility to hypotonic saline, leukocytosis during periods of active red cell regeneration, absence of hemoglobinemia, hemoglobinuria and hemosiderinuria, and by the characteristic febrile hemolytic crisis

Acquired hemolytic anemia may present a more difficult differential

problem In the acute fulminating type seen in children, Atkinson<sup>18</sup> found that hemoglobinuria has been reported in about 30 per cent of the cases Hemoglobinuria was not present even during acute hemolytic crises in the older patients reported by Dameshek and Schwartz<sup>19</sup> or by Mason<sup>20</sup> Spherocytic erythrocytes and increased fragility to hypotonic saline may or may not occur but are usually found during severe hemolytic crises<sup>10</sup> The major differences found in acquired hemolytic anemia are the acute or subacute onset, the severe febrile hemolytic crises, leukocytosis, increased red cell fragility to hypotonic saline, and spherocytosis during acute hemolytic phases<sup>10</sup>, hemoglobinuria only in severe hemolytic crises, if it occurs at all, and the absence of hemosiderinuria

Hemoglobinuria *ex frigore* is recognized by the relation of paroxysms to chilling and the positive Donath-Landsteiner reaction

March hemoglobinuria is easily ruled out by the fact that hemoglobinuria occurs only with physical exertion

Blackwater fever may occur in benign as well as malignant tertian malaria Foy and Kondi<sup>21</sup> succeeded in demonstrating the parasite in 40 per cent of their cases Thirty-three per cent showed *Plasmodium vivax*, 44 per cent *P. falciparum* and 14 per cent were mixed infections of *P. vivax* and *P. falciparum*

As already noted, case 2 was erroneously diagnosed blackwater fever because of the severe hemolytic crisis and hemoglobinuria (table 1) precipitated by relapses of benign tertian malaria The past history of hemoglobinuria will ordinarily lead to the correct conclusion Spherocytic erythrocytes are present in blackwater fever,<sup>22</sup> and hemosiderinuria has not been reported Cases of malaria tested in this hospital have shown no evidence of erythrocyte hemolysis in the Ham hemolysis tests

### SUMMARY

- 1 Two cases of hemolytic anemia with paroxysmal nocturnal hemoglobinuria are reported with full clinical and laboratory findings

- 2 The outstanding clinical features are anemia, icterus, hemoglobinemia, leukopenia, paroxysms of hemoglobinuria, persistent hemosiderinuria, tendency to vascular thrombosis, and a chronic unremitting course capable of persisting through many years Splenectomy, as well as other forms of known treatment, is of no value

- 3 Accelerated hemolysis occurs during acute infections and relapses of malaria as well as spontaneously and during sleep

- 4 Hemosiderinuria may be considered as indicating the existence of chronic hemoglobinemia exceeding the minimal renal threshold and reflects stuffing of the renal convoluted tubular epithelium with breakdown products of hemoglobin

- 5 The absence of spherocytic erythrocytes is in direct contrast to most

other types of hemolytic anemia and acute hemoglobinurias in which spherocytosis represents a phase in the process of erythrocyte disintegration and indicates a different hemolyzing mechanism is involved

6 The differential diagnosis has been discussed

#### BIBLIOGRAPHY

- 1 PIERCE, P P, and ALDRICH, C A Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome) Report of case with marked thrombocytopenia in five year old child, *Jr Pediat*, 1943, xxii, 30-42
- 2 WINTROBE, M W Clinical hematology, 1942, Lea and Febiger, Philadelphia
- 3 WITTS, L J Paroxysmal hemoglobinurias, *Lancet*, 1936, ii, 115-120
- 4 HAM, T H Studies on red blood cells Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria Investigation of mechanism of hemolysis with observations on five cases, *Arch Int. Med*, 1939, lxiv, 1271-1305
- HAM, G C, and HORAK, H M Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria Report of case with only occasional hemoglobinuria and with complete autopsy, *Arch Int Med*, 1941, lxvii, 735-745
- HAM, T H, and DINGLE, J H Studies on destruction of red blood cells Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria Certain immunological aspects of the hemolytic mechanism with special reference to serum complement, *Jr Clin Invest.*, 1939, xiiii, 657-672
- 5 HAMBERGER, L P, and BERNSTEIN, A Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, *Am Jr Med Sci*, 1936, cxcii, 301-316
- 6 SCOTT, R B, ROBB-SMITH, A H T, and SCOWEN, E F Marchiafava-Micheli syndrome of nocturnal hemoglobinuria with hemolytic anemia, *Quart. Jr Med*, 1938, vii, 95-114
- 7 ROSENTHAL, F Über eine neue Form von paroxysmaler Hamoglobinurie, *Ztschr f klin Med*, 1932, cxix, 449-459
- 8 ALTSHULE, M D, and GILLIGAN, D R Acute massive hemoglobinuria of obscure cause with jaundice and anemia, report of a case with clinical and hematologic studies and measurements of the blood pigment metabolism, *Arch Int Med*, 1941, lxviii, 957-978
- 9 FAIRLEY, N H Methemalbumin in man (pseudo-methemoglobin), *Proc Roy Soc. Med*, 1939, xxxii, 1278-1280
- 10 FAIRLEY, N H Fate of extracorpuscular circulating hemoglobin, *Brit Med Jr*, 1940, 213-217
- 11 GILLIGAN, D R, ALTSHULE, M D, and KATERSKY, E M Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions, *Jr Clin Invest*, 1941, xx, 177-187
- 12 YULE, C L Hemoglobinuria, *Physiol Rev*, 1942, xxii, 19-31
- 13 LICHT, J A, HAVILL, W H, and WHIPPLE, G H Renal thresholds for hemoglobin in dogs Depression of threshold due to frequent hemoglobin injections and recovery during rest periods, *Jr Exper Med*, 1932, lv, 603-615
- 14 NEWMAN, W V, and WHIPPLE, G H Renal thresholds for hemoglobin in dogs Hemoglobin injections and conservation of pigment by kidney, liver and spleen Influence of diet and bleeding, *Jr Exper Med*, 1932, lv, 637-652
- 15 BOGNIARD, R P, and WHIPPLE, G H Iron content of blood free tissues and viscera Variations due to diet anemia and hemoglobin concentrations, *Jr Exper Med*, 1932, lv, 653-665
- 16 HADEN, R L Hemolytic anemia, *Jr Lab and Clin Med*, 1940, xxvi, 65-81
- 17 DACIE, J V, and FIRTH, D Blood transfusions in nocturnal hemoglobinuria, *Brit. Med Jr*, 1943, i, 627-628
- 18 ATKINSON, F R B Lederer's anemia, *Brit Jr Child Dis*, 1940, xxxvii, 35-44

- 19 DAMESHEK, W, and SCHWARTZ, S O : Acute hemolytic anemia (acquired hemolytic icterus, acute type), *Med*, 1940, xiv, 231-327
- 20 MASON, V R : Acquired hemolytic anemia, *Arch Int Med*, 1943, lxi, 471-493
- 21 FOY, HENRY, and KONDI, ATHENA : Spleen puncture findings in blackwater fever, *Trans Roy Soc Trop Med and Hyg*, 1938, xxxii, 347-354
- 22 FAIRLEY, N H, and MURGATROYD, F : Recurrent blackwater fever induced by quinine, *Trans Roy Soc Trop Med and Hyg*, 1940, xxxiv, 187-194



tween this disease and the incidence of respiratory infections, for even though a severe epidemic of respiratory infections was present between December 1942 and March 1943, there was no increase in the number of cases of infectious mononucleosis.

### SYMPTOMATOLOGY

The incubation period varies between five and 15 days but the best evidence suggests that it is usually about 11 days.<sup>1</sup> Ninety per cent of the cases presented symptoms lasting from one to seven days prior to admission. The longest history given was two weeks and that in five patients. As will be seen in table 2, the majority of the cases complained of fever, sore throat,

TABLE II  
Symptoms on Admission

|                       |          |
|-----------------------|----------|
| Fever                 | 55 Cases |
| Sore throat           | 46 Cases |
| Malaise               | 35 Cases |
| Headache              | 15 Cases |
| Cough                 | 14 Cases |
| Adenopathy (cervical) | 13 Cases |
| Rhinitis              | 10 Cases |
| Dysphagia             | 6 Cases  |
| Sweats                | 3 Cases  |
| Anorexia              | 3 Cases  |
| Generalized aches     | 3 Cases  |
| Hoarseness            | 2 Cases  |
| Stiff neck            | 2 Cases  |
| Diarrhea              | 2 Cases  |
| Urticaria             | 2 Cases  |

malaise and headache. Two of the cases had their onset with pulmonary manifestations and were at first believed to be cases of primary atypical pneumonia. The blood counts and blood smears were normal on admission. One of the two cases showed a persistent low grade fever and developed a generalized adenopathy after complete resolution of the pneumonia and then developed a lymphocytosis with atypical lymphocytes and a positive heterophile agglutination test. The other case (described in more detail later) after complete resolution of the infiltrate in the right lower lobe developed a follicular tonsillitis, generalized adenopathy and fever with the typical blood smear findings six days after admission and a positive heterophile agglutination. As it is not unusual to find a normal differential count or even a polynucleosis early in this disease, it is quite possible that the pulmonary lesions were manifestations of the disease. A review of the chest roentgenograms of the two cases showed them to be in no way different from the cases of atypical pneumonia which have been seen here. Both were found to be in the lower lobe (one in the right and one in the left lower lobe) and both cleared in four and six days, respectively. Two patients complained only of "hives" and two others complained only of a diarrhea. All four of these patients had a generalized adenopathy which caused the

medical officer to suspect infectious mononucleosis. The majority of the other patients complained chiefly of a sore throat with an admission diagnosis of either nasopharyngitis or tonsillitis.

Fever was present in all but seven patients. It followed no particular pattern, was usually of the remittent type, and although it usually ranged between 101° and 102° F, in several cases it rose to as high as 104° F. As seen in table 3, the febrile state persisted for from one to 35 days. In 36

TABLE III  
Duration of Fever

|            |          |
|------------|----------|
| 0 Days     | 7 Cases  |
| 1-3 Days   | 15 Cases |
| 4-6 Days   | 18 Cases |
| 7-9 Days   | 11 Cases |
| 10-12 Days | 6 Cases  |
| 13-15 Days | 3 Cases  |
| 20-23 Days | 2 Cases  |
| 35 Days    | 1 Case   |

per cent of the cases it was present for more than six days. In view of the fact that most of the cases were admitted with a diagnosis of either an acute pharyngitis or an acute follicular tonsillitis, the charts of 60 unselected cases of pharyngitis and 60 cases of tonsillitis were reviewed. In both groups, the longest duration of fever was five days, and 87 per cent of the nasopharyngitis group and 80 per cent of the tonsillitis group had fever lasting three days or less. This is in marked contrast to the cases of infectious mononucleosis of which only 32 per cent had a temperature elevation for less than three days.

#### PHYSICAL EXAMINATION

On admission, the pharynx was found to be normal in seven cases, inflamed in 27 and associated with a follicular or membranous type of tonsillitis in 20 cases. In the nine other patients there was noted the development of an acute tonsillitis and generalized adenopathy from two to 10 days after admission to the hospital. Adenopathy was present in all patients during the period of hospitalization, involving the cervical nodes alone in 20 cases and being generalized in the others. Invariably the cervical nodes were larger than the others and were usually slightly tender. Thirteen of the patients were aware of enlarged nodes in the neck on admission to the hospital. The spleen was found to be enlarged in 16 of the patients; one was palpable three fingers' breadth below the costal margin, and the others were just palpable below the costal margin. Recent reports in the literature reveal a wide variation in the incidence of splenomegaly in infectious mononucleosis ranging from 10 to 90 per cent<sup>20, 21, 4, 1, 5</sup>. In addition to the two cases with urticaria, five others developed a transient maculopapular rash during the first week of hospitalization. Templeton and Sutherland<sup>5</sup> observed skin eruptions in 18 per cent of their cases and noted that the lesions



may be macular, maculopapular, scarlatiniform, may resemble erythema nodosum or may be urticarial in type. One of the patients developed jaundice.

A 21 year old white male, who had been in service for two years, was admitted on October 23, 1943, with a history of five days' duration characterized by a productive cough, malaise, and fever. Chest examination revealed slightly diminished breath sounds and subcrepitant râles in the right lower lobe. Chest roentgenogram on the day of admission revealed a small amount of scattered exudative infiltration at the right base. The white blood cell count was 5,100 with 24 per cent lymphocytes. His temperature dropped to normal in three days and a roentgenogram on the 1st day showed a complete resolution of the infiltrate. On that same day, October 24, 1943, the patient complained of nausea, and a fullness in his epigastrium, and vomited several times. He was then found to be jaundiced and an icterus index the following day was 36.3, the van den Bergh reaction was (direct) prompt positive, (indirect) 75 mg. On October 30, 1943, he first complained of a sore throat and examination revealed the tonsils to be enlarged, inflamed and covered with exudate. A blood count on November 3, 1943, showed 11,000 white blood cells with 62 per cent lymphocytes. On November 4, 1943, he was found to have a generalized adenopathy and both liver and spleen were palpable under the costal margins. On November 5, 1943, another blood smear was taken and the differential showed a total of 72 per cent lymphocytes, about half of them being of the atypical variety. A heterophile antibody test on November 7, 1943, was positive in a dilution of 1:1792. He ran a slight regular fever until November 20, 1943, by which time his jaundice had completely subsided and his liver and spleen were no longer palpable.

Cases of jaundice have been reported by others<sup>7, 8, 9, 1</sup>. Contratto<sup>7</sup> found 10 cases of jaundice in his series of 196 patients of infectious mononucleosis. No satisfactory explanation for the mechanism of jaundice in this disease was ever presented until the report of Ziegler<sup>6</sup> who described the postmortem findings in a case of infectious mononucleosis who died following a spontaneous rupture of the spleen. Microscopic examination of the liver revealed dilated and edematous sinuses containing the atypical lymphocytes. The small bile ducts were lined by swollen epithelial cells so that their lumina were diminished and some lumina appeared to be obliterated. In the focal infiltration, there was noted a destruction and disappearance of most of the liver cells. Likewise, there were noted focal lesions in the kidneys, lungs, and spleen with mononuclear infiltration, reticulum proliferation and necrosis, to suggest an acute infectious granulomatous process.

None of the cases presented any cardiac or renal symptoms nor were there any hemorrhagic manifestations, such as epistaxis, purpura or petechial hemorrhages.<sup>11</sup> Although several cases complained of headache, no case was encountered with involvement of the central nervous system,<sup>12, 13</sup> nor one in which the predominant complaint was abdominal pain.<sup>14, 15</sup>

#### LABORATORY FINDINGS

The leukocyte count varied from 3,900 cells to 48,000 cells per cubic millimeter. As seen from table 4, 44 per cent of the patients had a total white blood count below 11,000 cells. This wide variation in leukocyte

counts has been observed by all other observers and in itself is of little significance in making an accurate diagnosis. On the other hand, it is the findings of the blood smear which are so characteristic of the disease and upon which the diagnosis rests. In this series, the diagnosis was not made without what is considered a typical blood smear for this disease, namely, less than 40 per cent neutrophilic cells and the presence of so-called atypical lymphocytes, as originally described by Downey and McKinlay<sup>15</sup>. The differential count in this series revealed as few as 5 per cent granulocytes and as many as 61 per cent of the characteristic atypical lymphocytes. These abnormal cells vary greatly in size and shape. They possess a nucleus which may be oval, kidney shaped or slightly lobulated with the chromatin arranged in a coarse network. The cytoplasm is most frequently nongranular, basophilic and vacuolated in appearance. In 20 cases, successive blood smears at intervals of several days were found to be necessary before the characteristic changes were found, confirming the reports of others that several days may lapse before the appearance of the characteristic cells. An illustrative case is that of a patient admitted with a severe follicular tonsillitis with general-

TABLE IV  
Total Leukocyte Count on Admission

|               |          |
|---------------|----------|
| 3,000-7,000   | 11 Cases |
| 7,100-11,000  | 17 Cases |
| 11,100-15,000 | 15 Cases |
| 15,100-19,000 | 12 Cases |
| 19,100-23,000 | 5 Cases  |
| 23,100-29,000 | 2 Cases  |
| 48,000        | 1 Case   |

ized adenopathy, who appeared quite toxic and ran a fever between 102° and 104° F for two weeks in spite of a trial of sulfadiazine and penicillin. His white cell count on admission was 20,300 with 72 per cent polymorphonuclears and 27 per cent lymphocytes, none of which were atypical. Six days later, his white blood cell count was 48,000 with 19 per cent polymorphonuclears, 28 per cent lymphocytes, and 49 per cent atypical lymphocytes. A heterophile antibody test done the same day was positive 1:1792. The red blood cell count and hemoglobin were normal in all cases.

It has been known for a long time that serum of many normal persons is able to clump sheep erythrocytes in very low dilutions. Davidsohn<sup>16</sup> noted that high titers of heterophile antibodies were found in patients who had received injections of horse serum. Paul and Bunnell<sup>17</sup> in 1932 discovered a high titer of such antibodies in the sera of patients with infectious mononucleosis. Second in importance to the typical blood smear findings, this test when positive in significant titers, is considered to be diagnostic for infectious mononucleosis. Kaufman<sup>18</sup> considers a dilution of 1:32 by the Paul-Bunnell technic and one of 1:56 by the Davidsohn technic to be positive for the disease provided there have been no recent injections of horse serum. Mitchell and Zetzel<sup>2</sup> consider an agglutination of 1:112 to be diagnostic.

The Davidsohn technic has been used in our laboratory and it is believed that a dilution of 1:112 is diagnostic. As seen from table 5, 77 per cent of the cases had a positive heterophile agglutination. Two cases failed to show any agglutination (only one test was done) and the highest positive titer was 1:7168. The shortest period of time which lapsed between the onset of symptoms and the development of a positive agglutination was five days and the longest period, 51 days. Seventy per cent of the cases showed a positive agglutination within the first two weeks of their illness. In 10 patients, repeated tests had to be done before a positive titer was obtained. In nine cases who failed to show a positive titer, only one test was done. It seems likely that a higher percentage of positive titers would have been obtained if repeated heterophile studies had been made.

TABLE V  
Heterophile Antibody Test

|          |          |
|----------|----------|
| Negative | 2 Cases  |
| 1:28     | 10 Cases |
| 1:56     | 3 Cases  |
| 1:112    | 6 Cases  |
| 1:224    | 16 Cases |
| 1:448    | 13 Cases |
| 1:896    | 2 Cases  |
| 1:1792   | 5 Cases  |
| 1:3584   | 5 Cases  |
| 1:7168   | 1 Case   |

Blood Kahn tests were done on 26 cases and all were negative. This is in accord with the observations of Mitchell and Zetzel<sup>2</sup> and Halcrow, Owen and Rodger,<sup>19</sup> but in contrast to the experiences of other observers<sup>1, 20, 21</sup> who have noted that infectious mononucleosis can give transiently positive serological tests for syphilis. Kaufman<sup>20</sup> believes that the incidence of false positive reactions is between 2 and 10 per cent.

Chest roentgenographic examinations were done on 20 cases during the first few days of hospitalization before the correct diagnosis had been established in a search for possible clues as to the etiology of the persistent fever and all were normal. Blood cultures were taken on three patients and were negative. Sedimentation rates were done on six cases. One was normal and five were elevated. Throat cultures were taken on 17 patients and the usual flora was found to be present, namely, hemolytic and anhemolytic streptococci, *Staphylococcus albus* and *aureus* and *Neisseria catarrhalis*.

#### DISCUSSION

The causative agent of infectious mononucleosis is unknown. Pons and Julianelle<sup>22</sup> isolated a small gram-positive bacillus, *Listerella monocytogenes*, from the blood of one case which when injected into white mice produced an acute generalized infection. Kolmer,<sup>23</sup> on the other hand, demonstrated that it is not possible to produce a positive heterophile reaction in rabbits inoculated with cultures of *Listerella*. Van den Berghe et al.<sup>24</sup> suggested a virus origin of the disease. They injected blood of a patient with

infectious mononucleosis into a monkey and produced a febrile disease with leukopenia, a relative monocytosis and a high heterophile agglutinin titer in the serum. The condition was transmitted through several passages to other monkeys by the injection of blood, taken at the height of the fever, which was passed through a Seitz filter. Pearson<sup>25</sup> in a recent discussion on virus diseases, listed infectious mononucleosis as being caused by a viscerotropic type of virus.

The majority of the cases of infectious mononucleosis that have been reported have been found in children and in young adults. In a study of 196 cases reported by Contratto,<sup>3</sup> all of the patients were between 17 and 26 years of age. Eighty-one per cent of Bernstein's<sup>1</sup> cases were between 15 and 30 years. On the other hand, the older age groups are not immune to the disease. Halcrow<sup>19</sup> found the condition in a woman of 64 and a woman of 84 years of age. For some unknown reason, very few cases have been reported in the colored race.<sup>5, 27, 28, 29</sup> As far as could be determined, only 10 cases of infectious mononucleosis in the colored race have been reported in the literature. The following is a brief summary of the case record of the colored patient in this series.

A well nourished colored male was admitted to the Station Hospital on November 4, 1944, with the sole complaint that on the previous day he became aware of "lumps" in his neck. Examination was negative except for the presence of discrete, nontender cervical, axillary, inguinal and epitrochlear nodes. His temperature was normal. Blood serologic reaction was negative. Sedimentation rate was 25 mm in one hour. White cell count on admission showed 6,350 cells with 34 polymorphonuclears, 51 lymphocytes, 12 atypical lymphocytes and three monocytes. Heterophile antibody test on November 6 was positive 1:28. A subsequent blood count on November 13 showed it to be 5,300 with 43 polymorphonuclears, 31 lymphocytes, 16 atypical lymphocytes, 8 eosinophiles and 2 monocytes. A heterophile study on November 9 was positive 1:56 and on November 16 it had risen to 1:112. His course in the hospital was uneventful with gradual diminution in size of the lymph nodes and a normal temperature.

One of the most striking features of infectious mononucleosis is the wide variability in the type and severity of its symptomatology. The clinical picture rarely shows any constancy except when seen in the epidemic form. In the cases seen here the onset has varied from a mild one with minimal symptoms to one of acute prostration, high fever and profuse sweats, in which the diagnosis was not established until 10 days after the onset of the illness when the typical blood smear findings were obtained and in which the diagnosis was further confused by the presence of a marked eosinophilia (ranging from 13 to 21 per cent). Ringler and Hertz<sup>28</sup> described a case whose clinical course was characterized by recurrent chills and fever. The disease has been confused with nasopharyngitis, tonsillitis, Vincent's infection, diphtheria, agranulocytosis and leukemia. In addition, the diagnosis should also be considered in patients with unexplained fever, unexplained jaundice, splenomegaly, lymphadenopathy and in cases of lymphocytic meningitis. Probably the most constant findings were fever, an inflamed

pharynx with or without a tonsillitis, and adenopathy, either confined to the cervical chains or generalized. Tidy and Daniel<sup>10</sup> are of the opinion that infectious mononucleosis with no glandular enlargement is rare. Seventeen per cent of Contratto's series of 196 cases failed to show any enlargement of the peripheral nodes at any time during the course of the illness.

The basis for the final diagnosis and the pathognomonic feature of this disease is the finding of the atypical lymphocytes in the peripheral blood associated with a lymphocytosis. A positive heterophile antibody test, while desirable, is by no means essential. It is merely one point for the diagnosis, and if the clinical and hematological pictures are definite, it is believed that the diagnosis is established. The percentage of cases of infectious mononucleosis with negative sheep cell agglutination varies a great deal in different series of reported cases. Kaufman<sup>18</sup> explains this discrepancy on three factors: (a) the titer which the author considers necessary for a test to be called positive, (b) the frequency with which blood samples are tested in individual cases, (c) and most important, the number of cases of infectious mononucleosis which the author refuses to recognize and include as such because they have negative heterophile reactions. Thus, the percentage of cases with positive agglutination tests varies in different series from 43 to 100 per cent, most authors reporting 80 to 90 per cent. In Kaufman's series of 79 cases, 64 per cent were considered to have a positive heterophile test (1:56 or higher). Mitchell and Zetzel considered a titer of 1:112 to be positive and found this or higher titers in 72 per cent of their cases. Stuart<sup>31</sup> discussed an adsorption technic in performing the heterophile test based upon the differential absorption of the sheep cell agglutinins in the serum of different types of cases. It was noted that the sheep cell agglutinins in normal serum were absorbed by guinea pig kidney, and not by beef cells, the agglutinins in serum of patients with infectious mononucleosis by beef cells but not by guinea pig kidney, and agglutinins in the serum of persons with serum sickness by both guinea pig kidney and beef cells. Thus, by using the adsorption tests, the exact type of antibody present can be determined. In cases with a positive heterophile test in which the diagnosis of infectious mononucleosis is doubted, the adsorption technic is valuable.

Infectious mononucleosis has been considered a benign disease. However, in the past three years there have appeared in the American literature three cases of spontaneous rupture of the spleen<sup>7, 33, 34</sup> in infectious mononucleosis, two of whom<sup>33, 34</sup> recovered after splenectomy and the third of whom<sup>7</sup> died, that complication not having been recognized before death.

#### TREATMENT

There is no specific therapy for infectious mononucleosis. Rest in bed is most important during the febrile stage. Symptomatic therapy is all that has been found to be necessary in most of the cases. Penicillin was used in one case without improvement. Sulfadiazine was given to 12 cases. Seven



- 10 PAUL, J. R. Infectious mononucleosis, Bull New York Acad Med, 1939, **xv**, 43-55.
- 11 EPSTEIN, S. H., and DAMSHIEK, W. Involvement of the central nervous system in a case of glandular fever, New England Jr Med, 1931, **ccv**, 1238.
- 12 THELANDER, H. E., and SHAW, E. B. Infectious mononucleosis with special reference to cerebral complications, Am Jr Dis Child, 1941, **lxv**, 1131-1145.
- 13 STRAUS, R. Infectious mononucleosis simulating acute appendicitis with description of a specific lesion of the appendix, Am Jr Clin Path, 1942, **xii**, 295.
- 14 PHILIP, A. J. Infectious mononucleosis unusual case, New York State Jr Med, 1941, **xl**, 1664.
- 15 DOWNF, H., and MCKINLAY, C. A. Acute lymphadenosis compared with acute lymphatic leukemia, Arch Int Med, 1923, **xxxii**, 82.
- 16 DAVIDSOHN, I. Heterophile antibodies in serum sickness, Jr Immunol, 1929, **xvi**, 259.
- 17 PAUL, J. R., and BUNNELL, W. W. The presence of heterophile antibodies in infectious mononucleosis, Am Jr Med Sci, 1932, **clxxxiii**, 90.
- 18 KAUFMAN, R. E. Heterophile antibody reaction in infectious mononucleosis, Ann Int Med, 1944, **xxi**, 230-251.
- 19 HALCROW, J. P. A., OWEN, A. M., and RODGER, N. O. Infectious mononucleosis with an account of an epidemic in an Emergency Medical Service Hospital, Brit. Med Jr, 1943, **ii**, 443-447.
- 20 KAUFMAN, R. E. False positive serologic reaction for syphilis in infectious mononucleosis, Jr Lab and Clin Med, 1941, **xxvi**, 1439-1446.
- 21 SAPHIR, W. The Wasserman reaction in infectious mononucleosis, Am Jr Clin Path, 1939, **ix**, 306-310.
- 22 PONS, C. A., and JULIANELIE, C. A. Isolation of *Listerella monocytogenes* from infectious mononucleosis, Proc Soc Exper Biol and Med, 1939, **xl**, 360.
- 23 KOLMER, J. A. *Listerella monocytogenes* in relation to Wasserman and flocculation reactions in normal rabbits, Proc Soc Exper Biol and Med, 1939, **xlii**, 183.
- 24 VAN DEN BERGHE, L., LIESSENS, P., and KOVACS, L. Transmission de la mononucleose infectieuse humaine au Macacus rhesus, culture du virus en tissu, Compt-rend Soc de biol, 1939, **cxv**, 156.
- 25 PEARSON, E. F. Present concepts of virus diseases, Mil Surg, 1944, **xv**, 345-349.
- 26 LONGCOPE, W. T. Infectious mononucleosis with a report of ten cases, Am Jr Med Sci, 1922, **clxiv**, 781.
- 27 JOHNSON, R. D. Infectious mononucleosis in the negro, Jr Am Med Assoc, 1944, **cxv**, 1254-1255.
- 28 RAY, E. S., and CECIL, R. C. Infectious mononucleosis in the negro Report of three cases with one complicated by sickle cell anemia, South Med Jr, 1944, **xxvii**, 543-546.
- 29 RINGLER, S. H., and HERTZ, J. J. An unusual temperature course in infectious mononucleosis, Jr Lab and Clin Med, 1943, **xxviii**, 1445-1447.
- 30 TIDY, H. L., and DANIEL, E. C. Glandular fever and infectious mononucleosis, with an account of an epidemic, Lancet, 1923, **ii**, 9.
- 31 STUART, C. A., GRIFFIN, A. M., FULTON, M., and ANDERSON, E. G. Nature of the antibodies for sheep cells in infectious mononucleosis, Proc Soc Exper Biol and Med, 1936, **xxxiv**, 209.
- 32 KING, R. B. Spontaneous rupture of the spleen in infectious mononucleosis, New England Jr Med, 1941, **ccxix**, 1058.
- 33 DARLEY, W., BLACK, W. C., SMITH, C., and GOOD, F. A. Spontaneous splenic rupture in infectious mononucleosis A case and pathologic report, Am Jr Med Sci, 1944, **ccviii**, 381-384.
- 34 HOFFMAN, H. T., LEES, H. D., and COMROE, B. I. Use of sulfathiazole in infectious mononucleosis, Am Jr Med Sci, 1942, **cciii**, 731.
- 35 SMYTH, L. A. Report of a case of infectious mononucleosis, Cincinnati Jr Med, 1942, **xxiii**, 292.

## BRONCHOLITHIASIS: REPORT OF TEN CASES \*

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BRONCHOLITHS have been recognized in medical literature for centuries <sup>1</sup> In our time, with the impetus medical diagnosis has been given by improved technic in bronchology, roentgenology and biochemical analysis, this entity has changed its disposition from that of a medical curiosity to one of an accurately conceived disease Because of the relative infrequency with which this disease occurs, broncholithiasis has often been neglected in the differential diagnosis of bronchial obstruction As a result patients have found themselves erroneously classified among the more common diseases causing bronchial obstruction, thereby losing the advantage of an early diagnosis By such delay not only are complications which might have been avoided or minimized given time to develop, but the patient is at times submitted to unnecessary serious surgical procedures such as lobectomy or pneumonectomy when the true etiology is not discovered In presenting the following cases treated in the Department of Broncho-Esophagology of the Jefferson Hospital we would like to emphasize certain of the clinical findings so that they may be more readily recognized and more promptly treated

The term broncholithiasis has evolved out of a multiplicity of medical synonyms Other terms which are now sinking into disuse are pneumolith, pulmolith, bronchial stone or calculus, and lung stone or calculus By definition the term broncholithiasis signifies the condition in which calculi are formed in the bronchus This definition is somewhat limited in its scope since the pathogenesis of broncholithiasis may be extrabronchial as well as endobronchial

One cause of pathologic calcification in the lung is pathologic hypercalcemia or flooding of the blood with calcium This may be induced by overaction of the parathyroid glands or in conjunction with decalcifying diseases such as osteomalacia, general carcinomatosis of bone and multiple myeloma This variety known as metastatic calcification has not yielded any broncholiths to our knowledge It is more common for calcium to be laid down in dead or dying tissue, without any reference to the blood calcium level Calcium salts, most often the tribasic phosphate and carbonate, are deposited in the same proportion as found in a chemical analysis of bone When a broncholith is separated into its component parts the ratio of 85-90 per cent calcium phosphate and 10-15 per cent calcium carbonate is found <sup>2</sup>

The most likely sites for such calcification are caseous tuberculous areas

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in the pulmonary parenchyma or lymph nodes, in inspissated pus of an old abscess of the lung, and in a long standing empyema. Cartilages of the trachea and main bronchi are often calcified in the aged and on occasion have been found to contain bone marrow with a surrounding osseous structure.

The calculi vary in size, shape and consistency, but are usually hard, irregular, grayish white in color and frequently multiple. The size of those spontaneously expectorated is determined by the diameter of the eroded bronchus. Not uncommonly a concretion has been known to reach the lumen of a bronchus without being expectorated. It then acts as a foreign body firmly lodged in the airway causing bronchial obstruction and the sequelae commonly associated therewith. Inert areas of calcification may and frequently do exist in the lung without causing the patient any discomfort. When a calcific deposit becomes migratory, erodes through a bronchial wall and gains access to the airway, one is confronted with the disease broncholithiasis.

The most constant symptom associated with migration and expulsion of a concretion is cough and eventual expectoration of one or more calculi. The most alarming symptoms to the patient are substernal pain and hemoptysis. In every case there is usually a long history of recurrent respiratory infections preceding the acute illness which culminates in the diagnosis broncholithiasis.

The cough as experienced by every patient in this series was the result of bronchial irritation. Characteristically paroxysmal it was at first dry, hacking and productive of little or no sputum. More often it was worse at night when the patient assumed a prone position. Later when bronchial obstruction developed, suppuration and atelectasis became part of the symptom complex. Since the degree of obstruction was a variable depending mainly upon the size of the broncholith and the quantity of inflammatory tissue which developed at the site of bronchial erosion, complete atelectasis of the distal pulmonary parenchyma did not always occur. In every case, however, there was suppuration resulting in one to several ounces of purulent fetid sputum daily.

Every patient noticed bloody sputum at some time during his illness. Only rarely was massive hemorrhage reported. When bleeding of any measurable quantity did occur it was usually following bronchoscopic removal or spontaneous expulsion of a concretion. Hemostasis always ensued promptly and at no time was a transfusion required.

Thoracic pain was noted in one half the cases and most frequently was described as a tearing sensation just preceding expulsion of a concretion. Located substernally or deeply seated between the shoulders the pain never became severe enough to require morphine for relief. Weight loss, wheezing respiration, fever and dyspnea were not uncommonly noted in patients who had suppuration distal to the obstructing broncholith. Physical examination of the chest was not diagnostic and revealed changes in direct ratio to the degree of bronchial obstruction present.

The age of the patient did not seem to be significant since every decade from 20 to 70 was represented. There were five patients in the 30-40 group, two in the 60-70, and one in each of the others.

There was no evidence of active tuberculosis demonstrated by the roentgen studies in any of these cases. Multiple calcific shadows in the hilar areas with increased root markings were noted in a number of cases, but these changes were not sufficiently characteristic to warrant a diagnosis of broncholithiasis. In the completely obstructed bronchi atelectasis of the distal pulmonary parenchyma was present (figure 1). In four cases iodized



A

B

FIG 1 Roentgenogram (A) revealed atelectasis of the lower lobe of the right lung. The patient, male, aged 54 years, complained of cough, slight purulent expectoration and fever of 15 months' duration. At bronchoscopy an irregular broncholith (see figure 2, No 2553-C) was removed from the orifice of the right lower lobe bronchus.

Roentgenogram (B) made seven days following bronchoscopic removal of a broncholith revealed clearing of the right lower lung. Bronchographic studies showed an extensive cylindrical bronchiectasis.

oil was instilled after the obstructing broncholith had been removed. In each of these, cylindrical dilatations of the bronchi were outlined. These bronchiectatic changes were confined to the subdivisions of the airway distal to the obstruction created by the broncholith and consequently were considered a result of the existing disease.

A bronchoscopic examination was performed in each of the 10 cases presented as part of the diagnostic studies. In spite of spontaneous expectoration of a broncholith in 80 per cent of these patients bronchoscopic removal of one or more broncholiths was accomplished in five, or 50 per cent (figure 2). In one patient multiple concretions were removed during the first bronchoscopic examination. In another case one calculus was removed on each of two separate examinations within a period of a week. The remaining three cases yielded a single broncholith on the first examination.

Only two patients did not spontaneously expectorate a calculus either before or after the removal of a concretion bronchoscopically. Thus, it was of equal importance that an endoscopic examination be carried out for the patient who had spontaneously expectorated a calculus as for the patient who was suspected of harboring a broncholith. By this precaution an obstruction to the airway was not overlooked on the assumption that having expectorated a broncholith the patient was well.

Bronchoscopic examinations consistently demonstrated inflammatory changes characterized by injection and thickening of the mucous membrane throughout the tracheobronchial tree. In six cases (60 per cent) the exact site of erosion was identified by inflammatory stenosis of the bronchus. Grossly this obstruction appeared as an elevation of granulation tissue which

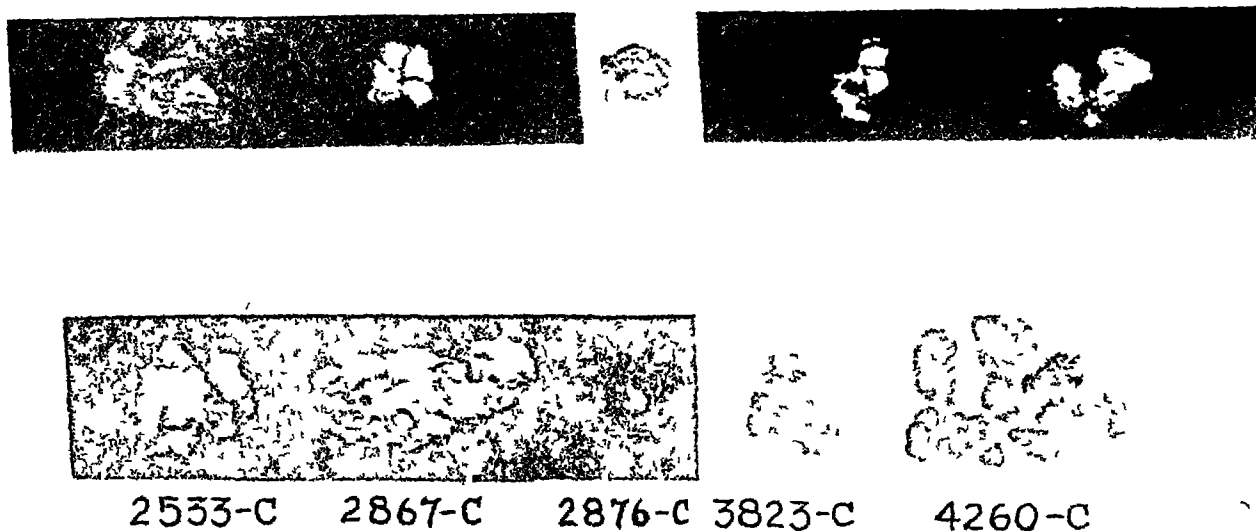


FIG 2 Photograph of broncholiths reproduced actual size. The upper row were expelled spontaneously by coughing. The lower row were removed bronchoscopically. FBDY No 2533-C was removed by bronchoscopy, in the case referred to under figure 1.

bled readily and frequently had the underlying firmness of a concretion upon palpation with bronchoscopic forceps. Distally there were purulent fetid secretions. In the remaining cases it was possible to identify the involved area by the presence of pus in the bronchial orifice and unmistakable inflammatory changes of the surrounding mucous membrane.

The most frequently involved lobe was the right middle in five cases. The right lower lobe was involved in three cases, the left upper and left lower lobes in one each. In four cases a biopsy was taken. Histologically each specimen was reported as inflammatory tissue. Repeated bacteriological examinations of the aspirated bronchial secretions failed to reveal tubercle bacilli.

Follow-up bronchoscopic examinations extended over an average period of 25 months. The interval between examinations was gradually increased from a few days to several weeks as the patient's general condition improved.

Once a broncholith was removed the inflammatory tissue noted on the initial examination receded to be replaced by smooth bronchial mucosa. Simultaneously atelectatic pulmonary tissue reexpanded. Permanent cicatricial narrowing of the bronchus was not found in any of the cases.

After a series of bronchoscopic treatments each patient experienced a definite reduction in cough and quantity of sputum per 24 hour period. As the cough and expectoration decreased, inflammatory changes in the lining mucous membrane of the bronchial tree also returned toward normal. Blood streaking disappeared in all patients after a few weeks. Every patient reported a gain in weight accompanied by a reduction in respiratory infections to two or three a year. It is interesting to note that the five cases who did not have a broncholith removed bronchoscopically enjoyed much the same improvement from bronchoscopy as those who had a frank foreign body.

One significant fact was the persistence of expectoration in the four proved cases of bronchiectasis, although the quantity of sputum was diminished to a few diams daily. In four other cases daily sputum did not entirely disappear and there was enough evidence bronchoscopically to strongly suggest bronchiectasis in the involved lobe.

There were two complications in addition to bronchiectasis. One patient developed a pleural effusion followed by a nontuberculous empyema and made a good recovery after surgical drainage by resection of a rib. A pulmonary abscess occurred in another case which responded favorably to surgical treatment.

Although 80 per cent of the patients gave a history of expectorating at least one broncholith before admission to the Clinic and half of this group had expectorated more than one broncholith, only one patient continued to expectorate small calculi after a series of bronchoscopic treatments.

### CONCLUSIONS

- 1 Broncholithiasis must be considered in the differential diagnosis of bronchial obstruction.
- 2 Productive cough, hemoptysis, substernal pain, and expectoration of a concretion are the salient clinical findings.
- 3 Bronchoscopy is the most satisfactory method of diagnosis and treatment.
- 4 Residual cylindrical bronchiectasis is the most common complication.

### BIBLIOGRAPHY

- 1 PAULALION, S. A. M. *Les pierres de poumon du pleure, etc.*, Thesis before Academy of Medicine, Paris, 1891, p. 364.
- 2 WELLS, H. G. Calcification and ossification, *Arch. Int. Med.*, 1911, vii, 721.

# AMEBIASIS: A REPORT OF THIRTY-NINE CASES OBSERVED IN AN ARMY GENERAL HOSPITAL STATIONED IN NORTHERN IRELAND<sup>\*</sup>

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DURING a 10 month period 39 cases of amebiasis were observed in an Army General Hospital stationed in Northern Ireland. It is significant, not only that the hospital was located in a temperate zone, but also that the onset of symptoms in the majority of these patients occurred while they were stationed in this region. Our experience emphasizes the fact that amebiasis is frequently a mild infection without the classical symptom of bloody diarrhea, without proctoscopically visible ulceration, and without demonstrable motile amebae in the stools or bowel wall scrapings.

When World War II is over, a large portion of our armed forces will have served, at one time or another, in areas endemic for amebiasis, and under conditions favorable to the acquisition of infection. These men and women will return to all parts of the United States. The long incubation period of the disease, its insidious onset, the mild nature of its symptoms in many cases, the long symptom-free remissions, and its tendency to recur even after treatment, all imply that many of these individuals will be encountered in post-war civilian practice. Cross-infection does and will occur, even in temperate areas, and the potential menace of the passer of ameba cysts, whether he is a symptomless carrier or a mild and unrecognized case of amebic infection, will also demand increasing consideration in the post-war era.

It is the purpose of this report, therefore, to stress some of the clinical aspects of the cases studied, which have proved to be of value in diagnosing the infection.

## EPIDEMIOLOGY

The source of infection in these cases could not be definitely established. Twenty-six patients had spent a period of time, either in civilian life or in Army training, in the Southern parts of the United States where amebiasis is endemic. One patient had had Army training in Panama. The other 12 patients had all had contact, through mess and latrine facilities, with some one of the original 26.

Twenty-six patients were members of one Division. A survey of stools of the food-handlers of this Division revealed an incidence of about 20 per

<sup>\*</sup> Received for publication February 15, 1945

cent cyst carriers.\* The Division was composed largely of soldiers from southern states, and it had been through maneuvers in both Tennessee and Louisiana. This evidence suggests that the original infections occurred in these endemic areas, and that through carriers there was subsequent cross-infection.

### SYMPTOMS

The outstanding feature of the clinical picture in this group of patients was the mild nature of the symptoms which they presented. The commonly described bloody diarrhea of amebic dysentery was evident on admission in only seven cases, and in the past histories of only two others. In fact, 13 of these patients were admitted to the hospital with diagnoses other than colitis or amebiasis, the disease being discovered incidentally while they were under observation.

Careful inquiry into the gastrointestinal history of each patient revealed a clinical story which fell into one of the three following categories. One group of nine patients had the classical picture of intermittent bouts of bloody diarrhea and crampy abdominal pain, associated with malaise, fever, and some loss of weight. A second group, comprising 28 patients, complained of mild short bouts of watery diarrhea or loose, soft stools, vague abdominal pain or soreness, audible peristalsis, and gradually increasing fatigue. In the third group of two patients, intermittent constipation was the outstanding symptom, and was accompanied by some abdominal pain and increasing fatigue.

Each of these symptoms is of sufficient significance to warrant individual attention. Their frequency is indicated in table 1.

TABLE I  
Frequency of Symptoms in 39 Cases of Amebiasis

|    |                     |    |
|----|---------------------|----|
| 1  | Diarrhea            | 36 |
| 2  | Abdominal pain      | 35 |
| 3  | Nausea              | 11 |
| 4  | Audible peristalsis | 10 |
| 5  | Loss of weight      | 10 |
| 6  | Bloody diarrhea     | 9  |
| 7  | Vomiting            | 8  |
| 8  | Fatigue             | 7  |
| 9  | Constipation        | 5  |
| 10 | Fever               | 4  |
| 11 | Chest pain          | 2  |

*Diarrhea* Diarrhea, noted in the histories of 36 patients, was the symptom most frequently encountered. As mentioned above, only nine patients had had a frankly bloody diarrhea. The typical picture presented by the other 27 was one of short bouts of four to eight watery or loose bowel movements a day, gradually increasing in frequency and severity. Between these bouts the bowel habit occasionally returned to normal, but more fre-

\* From the Laboratory Service of Lt Col Morris L Rakieten, Mcd Corps, AUS

quently the patient had two to four semiformal stools daily. At times, constipation alternated with diarrhea.

Since short bouts of watery diarrhea were an extremely common complaint among Army personnel, the significance of this symptom frequently went unrecognized for some time. In these patients, however, each bout was either longer or more severe than it was in other members of their units. Furthermore, they did not have the prompt return to a normal bowel habit that is the common experience with non-specific diarrhea.

*Abdominal Pain* The symptom of abdominal pain occurred second in frequency, appearing in the histories of 35 patients. It varied in intensity from the marked cramps associated with severe diarrhea, to vague abdominal discomfort. When crampy in nature it was usually widespread over the whole abdomen, but occasionally was limited to one quadrant. It was frequently expressed by the patient as "gas pain." It was intermittent in character, and usually varied in direct proportion to the severity of either diarrhea or constipation. An occasional patient complained only of abdominal soreness, most commonly in the right lower quadrant.

The incidence of other symptoms noted in this series of cases dropped off sharply in comparison with the first two. Two of these other symptoms, audible peristalsis and fatigue, probably had a higher incidence than the figures indicate, because they were not emphasized in history-taking among the first half of the patients. They were outstanding enough in more recent cases to deserve comment.

*Audible Peristalsis* One of the earliest symptoms complained of by at least 10 patients was abdominal rumbling, so much so that it was frequently embarrassing to the patient. It occurred as a rather constant symptom whether diarrhea and pain were present or absent.

*Fatigue* By far the most prominent constitutional symptom was fatigue. The patient complained of gradually increasing tiredness at the end of the ordinary working day. Occasionally, he became completely exhausted by a day's work which usually would not have affected him. This symptom in several instances was the one which made the patient seek medical attention. It tended to increase steadily, and was frequently accompanied by sleepiness. Patients who were unaccustomed to taking naps found that they could sleep at any time, and that their sleep was not as refreshing as it had been normally.

*Other Symptoms* Nausea and vomiting were more often encountered than would be expected, since the pathological process takes place in the colon. They were sporadic in occurrence, however, and did not affect the patient's appetite.

Fever should be mentioned because of its low incidence. Febrile episodes were experienced by only four patients. This fact emphasizes the low-grade character of the infection.

*Appendicitis* During the symptomatic period of the amebiasis, three

of these patients developed symptoms of appendicitis and had appendectomies performed. One other patient was admitted to the hospital as a possible case of appendicitis, and only after observation was the diagnosis of amebiasis made. This finding is in accord with the experience of others. Clark<sup>1</sup> states that the cecum is involved in 87.3 per cent of cases of amebiasis, and that concomitant appendicitis is usually the result of invasion of the appendix by the *E. histolytica*.

*Acute Enteritis* It is known that an acute enteritis occasionally acts as the trigger mechanism to initiate the symptom complex of amebiasis. In three of these patients this sequence of events took place. The organism isolated in two was *Salmonella montevideo*. The undue persistence of symptoms in such a patient should indicate an investigation for *E. histolytica*. Apparently the acute inflammation enhances the invasiveness of a latent amebic infection. This has been demonstrated experimentally in kittens (with croton oil and certain bacteria) by Nauss and Rappaport.<sup>2</sup>

*Duration of Symptoms* The period over which these patients experienced symptoms varied from one week to seven years (table 2). One pa-

TABLE II  
Duration of Symptoms in 39 Cases of Amebiasis

|                          |    |
|--------------------------|----|
| Three months or less     | 16 |
| Three months to one year | 11 |
| More than one year       | 12 |

tient had had symptoms referable to his colon since childhood, and it was impossible to designate the date of onset. In 27 patients the duration of symptoms was one year or less, and in 16 it was three months or less. All patients, except those who had had symptoms for two months or less, had noted remissions and exacerbations. The remissions were characterized by a sense of well-being sufficient to make the patient put off seeking medical attention.

### PHYSICAL SIGNS

It is notable that the general appearance and nutrition were appreciably altered in only three of these patients. These three appeared emaciated and toxic. All had bloody diarrhea.

The most significant physical findings were observed in the chest, abdomen, rectum, and rectosigmoid regions (table 3).

*Chest Findings* Nine patients had abnormal physical signs in their chests. Six had coarse râles and wheezes audible bilaterally, and in one of these there was also an impaired percussion note at the right base. Another patient showed a slightly impaired note and suppressed breath sounds at the right base. The other two revealed signs of a pleural effusion, one on the right side, and the other bilaterally.

The significance of these findings is somewhat confused by the high incidence of primary atypical pneumonia among Army personnel in this region.



In four of these patients, however, the chest signs were believed to have been due, at least in part, to diaphragmatic irritation associated with an amebic hepatitis. Further discussion will appear under this heading.

*Abdominal Findings* The outstanding abdominal sign was tenderness. It appeared in 31 patients. There was considerable variation in its intensity, but it was severe in only one instance. It was usually located somewhere along the course of the colon, most frequently over the descending colon or the cecum. In one patient a tender mass was felt in the left lower quadrant, due to pericolic inflammation and abscess following perforation of an amebic ulcer. This receded with emetine therapy.

The liver was palpable one centimeter or more below the costal margin in six of these patients, but was tender in only one.

*Proctoscopic Findings* Only four patients exhibited the typical proctoscopic picture of amebic dysentery, i.e., sharply punched-out ulcer craters

TABLE III  
Physical Findings in 39 Cases of Amebiasis

|   |  |    |
|---|--|----|
| 1 | Abdominal tenderness                               | 31 |
| 2 | Palpable liver                                     | 6  |
| 3 | Fever  | 4  |
| 4 | Emaciation   | 3  |
| 5 | Signs of a pleural effusion                        | 2  |
| 6 | Proctoscopic findings                              |    |
|   | <i>a</i> Mild proctitis                            | 17 |
|   | <i>b</i> Normal rectum and rectosigmoid            | 12 |
|   | <i>c</i> Ulceration with normal mucosa intervening | 4  |
|   | <i>d</i> Ulceration with generalized proctitis     | 3  |
|   | <i>e</i> Mucosal hemorrhages                       | 3  |

with normal mucous membrane intervening. Three others showed ulceration, but with considerable generalized inflammation of the rectal mucosa. Of these seven patients, only five had a history of bloody diarrhea. In one of these cases with extensive ulceration, there had been perforation in the rectosigmoid area with secondary infection and communication with an extracolonic inflammatory mass. Following emetine-carbarsone-chiniofon therapy the ulcerations healed, but stricture and mucosal polyps developed. In this case biopsy showed no malignant change.

Three patients had minute mucosal hemorrhages of the rectum, possibly beginning evidence of ulceration. Seventeen revealed a mild diffuse proctitis without evidence of ulceration, the remaining 12 patients had no abnormalities visible on proctoscopic examination.

During proctoscopy warm-stage microscopic examination was made of scrapings from the rectal or sigmoid mucosa. In eight cases motile trophozoites were observed (table 4), and in three others forms resembling dead trophozoites were seen, although the diagnosis was never based on this finding. With but one exception trophozoites were found in all patients who showed ulceration. In 28 patients cysts of *E. histolytica* were found in the contents of the rectum and sigmoid aspirated at proctoscopy.

## LABORATORY DATA

*Stool Examination* The stools were soft or watery. The presence of blood was the exception rather than the rule. In cases suspected of having amebiasis meticulous search was made for trophozoites or cysts of *E. histolytica* in at least three stools before the diagnosis was discarded. Many more stools were examined, however, when the symptoms were at all suggestive. Even with this careful technic, it is very likely that some cases remained unrecognized. Cysts were found in the stools of 26 patients (table 4). Charcot-Leyden crystals, to which there has occasionally been attached some diagnostic significance, were seen in only one stool. In the other 13 patients either cysts or active amebae were found in specimens taken at proctoscopy. A diagnosis of amebiasis was made only when the organisms were observed in either the stool or proctoscopic specimen.

*White Blood Cell Count* White cell counts were made on the blood of 25 patients. They ranged from 6,050 per cu mm, to 23,300 per cu mm, the mean being 10,140 per cu mm. The polymorphonuclear leukocytes

TABLE IV  
Location and Form of *E. histolytica* Found in 39 Cases of Amebiasis

|  |    |
|--|----|
| 1 Motile trophozoites and cysts in proctoscopic specimen, cysts in stool                   | 4  |
| 2 Motile trophozoites and cysts in proctoscopic specimen, no cysts in stool                | 2  |
| 3 Motile trophozoites in proctoscopic specimen, no cysts in proctoscopic specimen or stool | 2  |
| 4 Cysts in proctoscopic specimen and stool, no trophozoites                                | 19 |
| 5 Cysts in proctoscopic specimen, not in stool   | 1  |
| 6 Cysts in stool, not in proctoscopic specimen   | 11 |

varied from 44 per cent to 90 per cent, the mean being 66 per cent. There was no correlation between the severity of the infection or the incidence of complications and the height of the white cell count.

*Pleural Fluid* Fluid was withdrawn from the chest of one of the two patients who had a pleural effusion. It was serofibrinous, had a specific gravity of 1.016, a white cell count of 1,600 per cu mm, of which 100 per cent were lymphocytes. Amebae could not be found in a centrifuged specimen.

*Roentgenographic Examination* Roentgen-ray studies\* by barium enema were made on 20 patients. Sixteen of these showed a spastic deformed cecum, both on fluoroscopy and on the films. This finding is not surprising in view of the high incidence of cecal involvement in amebiasis.

Post-therapy barium enemas were performed on nine patients, eight of whom had shown cecal deformity at the onset of treatment. In three the deformity had disappeared. In the others no change had taken place. Since this procedure was carried out immediately after the cessation of chiniofon therapy, it is not surprising that the incidence of improvement was low.

Fluoroscopy and films of the chest revealed, in three patients, an elevated sluggish right diaphragmatic dome, in two of these there was also a right-

\* From the Roentgenological Service of Capt. Peter J. Gianquinto, Med. Corps, AUS.

sided pleural effusion. These findings, since they appeared in the absence of any active pulmonary parenchymal lesion, were considered to be indicative of hepatic involvement.

### HEPATITIS

The diagnosis of amebic hepatitis was based on the following criteria: 1 Demonstration of the organism in stools or proctoscopic specimens. 2 An enlarged liver, as evidenced by palpation or an elevated right diaphragmatic dome. 3 Pleural thickening or fluid in the right costophrenic sinus, in the absence of pneumonia. Seven patients were believed to have hepatic involvement. In six the liver was palpable one centimeter or more below the costal margin. In three the right dome of the diaphragm was high and limited in motion. Two of these three had a pleural effusion at the right base. It is interesting to note that it was the roentgen-ray and fluoroscopic findings of a high right diaphragmatic dome, and pleural effusion in the right costophrenic sinus, that first suggested the diagnosis in these two cases.

Liver function tests performed on four of these patients were normal.

It is significant that only one of these patients had had symptoms of amebiasis for more than eight months, and three had had symptoms for less than three months. This finding emphasizes the fact that hepatitis is not necessarily a late complication of the disease.

Hepatic abscess was suspected but not proved in one case.

### THERAPY AND DISPOSITION

This group of patients cannot be used as an index of the efficacy of antiamebic therapy, because follow-up studies could not be carried out. Treatment consisted of either one or two courses of carbarsone, 0.25 gram t.i.d. for seven days, and chiniofon, 1.0 gram t.i.d. for seven days. In addition, on five alternate days retention enemas of either carbarsone, 2.0 grams in 200 c.c. of a 2 per cent sodium bicarbonate solution, or chiniofon, 4.0 grams in 200 c.c. of distilled water, were given in most cases. Many of the patients not receiving emetine were ambulatory during treatment.

Emetine hydrochloride, 0.3 gram b.i.d. for six to 10 days, was usually reserved for patients with frank dysentery or hepatitis, and was administered simultaneously with carbarsone. Thirteen patients received emetine. Electrocardiograms were recorded before therapy was started, and on the fifth day. In one the toxic effect of the drug was manifested by lowering of the T-waves in all leads, a finding which reverted to normal five days later.

The well-known irritative effects of chiniofon, diarrhea and rectal burning, were noted by a majority of the patients. Carbarsone did not produce any toxic effects.

The immediate results of therapy appeared to be satisfactory. Diarrhea decreased in severity, and rectal and lower sigmoid ulcerations healed rapidly.

It was unusual, however, for a patient to leave the hospital entirely free of his symptoms. There were no deaths.

The disposition of these patients at the termination of hospitalization gives some indication of the rapidity of response to therapy. Twenty-two patients were returned directly to full duty. Nine were sent to the Rehabilitation Ward for two weeks before returning to duty. One patient was sent to a Rehabilitation Hospital following an arthrotomy, his amebiasis having been incidental to a knee injury. The average duration of hospitalization for those patients returned to duty was 33 days. It was necessary to send five patients, four of whom had hepatic involvement, to the Zone of the Interior for further therapy and convalescence. One patient was sent to the Zone of the Interior because of non-union of fractures of the tibia and fibula, and another because of mental deficiency. There were only five patients, therefore, who, as far as their amebiasis was concerned, were not fit for full duty on the completion of one or two courses of therapy and a short period of rehabilitation.

#### DISCUSSION

This study of amebiasis serves not to disclose any new aspect of the disease, but rather to emphasize some of its less familiar characteristics.

The predominance of mild symptoms of relatively short duration and the extremely low incidence of a history of bloody diarrhea were remarkable. Intermittent, low-grade, slowly progressive changes in bowel habit proved to be a significant finding, and warranted an all-out search for the organism. The frequency of visualizing a normal or only slightly inflamed rectal and lower sigmoid mucosa on proctoscopic examination was striking. In these cases, active trophozoites were, of course, rarely observed, and the diagnosis had to be established by the discovery of cysts in the stool or colonic scrapings.

Manson-Bahr<sup>3</sup> states: "There is a large class of cases which may be labeled 'amebic diarrhea,' because, in the whole course of the illness, none of the more familiar symptoms of dysentery make their appearance." The truth of this statement is well illustrated by this group of patients. In any mild colonic disorder, even one of relatively short duration, amebiasis should be included in the differential diagnosis. The failure to find trophozoites is not enough to exclude the infection, since they are almost always absent in this type of case. Cysts must be searched for in fresh and iodine-stained stool smears. For routine clinical use we feel that three stool examinations, carefully made, are sufficient in most instances. In view of the known variability and intermittency of cyst passage, however, this rather arbitrary standard should be exceeded, if the symptoms are at all suggestive. In fact, the more suggestive the symptoms are, the greater the number of negative stools that should be required to exclude the diagnosis.

Those patients with amebic hepatitis illustrate the fact that it is not

unusual for the liver to become involved within a few months of the onset of symptoms. A high sluggish right diaphragmatic dome, and serofibrinous pleural effusion in the right costophrenic sinus are of considerable significance in the diagnosis of this complication. Determination of the presence of hepatitis is important from the standpoint of treatment, since emetine is still considered to be the most effective therapeutic agent for the hepatic infection.

When our Armed Forces return home amebiasis, like malaria, will probably frequently be encountered in veterans with overseas service. It is believed that this group of cases serves as a preview of what may be expected in post-war civilian practice, and it is hoped that it will direct more attention toward the recognition of this type of amebiasis.

### SUMMARY

1. A report has been presented of 39 cases of amebiasis observed in an Army General Hospital stationed in Northern Ireland.

2. Emphasis has been placed on the clinical picture portrayed by these patients. It was characterized principally by

- a. The frequent onset of symptoms in a temperate region
- b. The mild nature of the symptoms
- c. The low incidence of bloody diarrhea
- d. The prevalence of an intermittent, low-grade change in bowel habit, most frequently in the form of a watery diarrhea or loose stools
- e. The low incidence of proctoscopically visible ulceration and motile trophozoites
- f. The early involvement of the liver in some cases

3. The report serves as a preview of the type of amebiasis which may be encountered in post-war medicine, and emphasizes the need, particularly in temperate regions, for more prominent consideration of the disease in the differential diagnosis of mild colonic disorders.

### BIBLIOGRAPHY

1. CLARK, H. C. Distribution and complications of amebic lesions found in 186 postmortem examinations, *Am. Jr. Trop. Med.*, 1925, v, 157.
2. NAUSS, R. W., and RAPPAPORT, I. Studies on amebiasis—pathogenesis of mucosal penetration, *Am. Jr. Trop. Med.*, 1940, xx, 107.
3. MANSON-BAHR, P. The dysenteric disorders, 1943, Cassell & Company, Ltd., London, p. 161.

# HYPERSENSITIVITY AND RHEUMATIC FEVER. PART I\*

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## PART I

- A Evolution of the basic concepts of hypersensitivity
  - 1 Anaphylaxis
  - 2 Arthus phenomenon
  - 3 Serum sickness
  - 4 Properties of allergy
  - 5 Von Pirquet's concept of the deleterious effects of antibodies
  - 6 Nature of the antigen-antibody reaction
- B Relation of allergy to immunity

## PART II

- A Relation of rheumatic fever to hypersensitivity
  - 1 Clinical and pathological evidences
  - 2 Immunological evidences
- B Rôle of salicylates in rheumatic fever
- C Immunization against rheumatic fever
- D Discussion

## PART I

### EVOLUTION OF THE BASIC CONCEPTS OF HYPERSENSITIVITY

THE Greeks and the Romans recognized the condition of hypersensitivity and described the phenomenon under the term "idiosynkrisie," a word still in use today. Our knowledge of allergy had its true beginning, however, in the early part of the twentieth century. Although Koch, in 1890, had clearly demonstrated in his experiments with tuberculin the phenomenon of hypersensitivity to a specific substance, he did not realize that he had stumbled on a new phenomenon. In 1894 Flexner, Arloing and Courmont had observed the same phenomenon, but it was not until 1902 that the French physiologist, Charles Richet,<sup>1,2</sup> recognized its novelty and followed his observations to their logical conclusions.

*Anaphylaxis* Richet's discovery was made when he attempted to immunize dogs with toxins. He injected 0.1 c.c. of a glycerine extract of the tentacles of actinaria into dogs. When, 22 days later, a second injection of the same amount was made, the dog was "in a few seconds extremely ill. breathing became difficult, and he was panting. He could scarcely drag himself along, lay on his side, was seized with diarrhea, vomited blood, sensibility diminished, and he died in 25 minutes." Richet then concluded

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that the first toxin injection not only caused no antitoxic immunity but produced an increase in the sensitivity to toxin which became evident after a certain incubation period. The first toxin injection did not act "prophylactically" in these animals but, in contrast, as he termed it, "anaphylactically" (without protection). Richet also found that if the animal survived the second injection, it recovered from its effects in a shorter time than after a first injection. He stated that two different substances were contained in the toxin—one concerned in establishing an immunity, the other producing a hypersensitiveness. The separate existence of these two substances has long been questioned.

*Arthus Phenomenon* In 1903 Arthus showed that non-toxic protein may also produce hypersensitiveness. He observed that rabbits did not react to a primary injection of horse serum, whether subcutaneous, intraperitoneal, or intravenous. When rabbits previously sensitized to horse serum, however, were given an intravenous injection of the serum, very severe symptoms appeared almost immediately, which could lead to anaphylactic death in two to four minutes. If the horse serum was injected subcutaneously at six day intervals, absorption of the serum took place after the first three injections. After the fourth injection, however, local infiltration occurred and was followed by necrosis, sloughing and abscess formation. This reaction Arthus described as "local anaphylaxis." It is known today as the "Arthus phenomenon."

*Serum Sickness* Since Pasteur's discovery that certain diseases are caused by infectious agents, attempts have been made to aid the body in combating the invading bacteria and accelerating the mechanism of immunity. Antitoxic and anti-bacterial sera obtained from other animal species have been used for this purpose. Von Behring in 1894 introduced the treatment of diphtheria with antitoxic horse serum. It was soon noticed that exanthem sometimes followed the injection of a therapeutic serum and was accompanied by a high fever and multiple painful joint swellings. It was experimentally proved that these sequelae were not produced by the antitoxic content, but by something inherent in the horse serum itself, since the same symptoms were produced in non-diphtheritic persons by normal horse serum.

Up to this point all the observations had been recorded without any attempt at interpretation. Von Pirquet and Schick<sup>3</sup> in 1905 were the first to analyze the condition critically. They gave the name "serum disease" to the symptoms which follow the first injection of horse serum, usually in eight to 12 days. This disease is characterized by fever, leukocytosis, an elevated sedimentation rate, edema, erythema and urticaria, arterial hypotony, swelling of the liver, spleen, and lymph nodes, swelling of the joints, muscular pain, albuminuria, enteritis, and, in rare cases, a local reaction at the site of injection, resembling the Arthus phenomenon. Von Pirquet and Schick explained the manifestations as follows. Foreign serum acts on

man as an antigen. Antibody, which develops in the organism as a result of the antigen, produces the symptoms upon union with the horse serum. Serum sickness is, therefore, an *in vivo* antigen-antibody reaction which depends upon the appearance of the antibodies while horse serum still remains in the blood.

Von Pirquet and Schick also noted that reinjection of serum at some later date results in immediate and accelerated reactions, which phenomenon they called "allergy" (altered reactivity). At first the term was synonymous with "anaphylaxis," but Richet considered anaphylaxis only from the standpoint of hypersensitiveness to foreign proteins, whereas von Pirquet in his term "allergy" included all reactions to foreign proteins and infectious agents and laid the groundwork for our understanding of the relationship between allergy and immunity.

*Properties of Allergy* Von Pirquet and Schick then extended their concept of altered reactivity to include all infectious diseases and analyzed them from three standpoints: (1) allergy according to time, (2) quantitative allergy, and (3) qualitative allergy. They reached the conclusion that in most of the infectious diseases which they studied the clinical reaction was not an immediate consequence of the infection, but was a more complicated phenomenon than the mere action of some microorganism or some other foreign substance on the tissues and that it involved the existence of a third factor—altered reactivity of the tissues of the host. This third factor varied as to *time*, *quality*, and *quantity*. They noted that with relation to *time*, reactions tended to occur in three groups.

In group I, the reaction appears after eight to 12 days. In this group fall the spontaneous infectious diseases such as smallpox, measles, whooping cough, chickenpox and others, as well as artificial infections on the skin, as with vaccinia. The same phenomenon is seen after injection of horse serum into man (serum sickness).

The clinical manifestation of disease, these workers concluded, is not the only reaction belonging in this group. The formation of certain antibodies and the appearance of a change in reactivity involve the same time element. After intravenous injection of horse serum into a rabbit, precipitating antibodies are not present for eight to 12 days, following injection of foreign protein into a guinea pig, a state of hypersensitivity toward the protein appears within a similar interval of time.

In group II, the reaction appears after three to seven days. In this group belong revaccinations done several years after the initial vaccination. When an injection of horse serum in man or animal is followed, after a long interval, by another injection, the time of precipitin formation is shortened and the clinical manifestations appear sooner.

In group III, the reaction appears immediately. This group comprises the anaphylactic reaction following a second injection of serum some weeks after the initial injection. Within a few minutes urticaria, edema, and signs of collapse appear.



There were also *quantitative* and *qualitative* differences in the reaction. The intensity of reaction varied widely. First infections with a small number of microorganisms were followed by a far more intense reaction than the subsequent infections (after the development of immunity). On the other hand, if the injection was performed a second time, the immediate reaction was of startling intensity (allergy).

As for the differences in the *quality* of reaction, it was found that a second infection with tuberculosis, for instance, leads to only a local inflammation instead of the generalized effect of the first infection (inhibition of spread?).

Two other phenomena were noted.

(1) The change in reaction could be transmitted from one animal to another with serum (temporary immunity due to passive transfer of antibody).

(2) If an animal which had acquired the property of immediate reaction was injected with a large amount of the material to which it is susceptible, it was not able to react to subsequent injections for several days (rapid desensitization).

*Von Pirquet's Concept of the Deleterious Effects of Antibodies* Von Pirquet explained the phenomena of serum sickness as follows. The first episode of serum disease could not be due directly to any constituent of the injected serum, but to the fact that the animal took part in the reaction with the formation of an antibody. The presence of this antibody would then lead to an immediate "in vivo" reaction on a second injection. The reaction in either case would result from a toxic compound formed by the combination of the antibody with the horse serum. This explanation involved a new conception of an antibody. Previously an antibody was considered a protective substance, the action of which neutralized completely the antigen. Von Pirquet's hypothesis was that these other antibodies form a new toxic compound with the antigen. The important principle of this new conception lay in the suggestion that a disease might be due indirectly to an antibody.

Thus, according to Von Pirquet, serum disease is caused by the toxic compound formed when antigen and antibody meet. When the antibody arises eight to 12 days after the first injection of serum, symptoms of general disease occur. These symptoms are due to toxic bodies formed by the breakdown of the allergen through the antibody. With the first injection, the horse serum was present first and antibody developed later. Therefore, symptoms were delayed. With reinjection, the antibody is already present and the toxic body is formed immediately. Thus, an immediate reaction is elicited.

In rabbits, the manifestations of serum disease following the first injection must be below the level of clinical observation. On reinjection, the immediate reaction is manifest as anaphylaxis. If reinjection is delayed several months, the precipitin has probably disappeared from the rabbit's blood.

However, with reinjection, antibody appears as early as the sixth day. This is the "accelerated reaction," for the production of antibodies.

In man, if a reinjection of horse serum is performed shortly after the first injection, antibodies may still be present. The serum then reacts first with the existing antibodies and the toxic substance thus produced causes an immediate reaction. The excess of antigen, however, induces the formation of more antibodies in a period of four days. The antibodies then destroy the remainder of the horse serum, and the result is again a toxic reaction, an "accelerated serum disease." During that interval in which antibody is absent, a repetition of the horse serum injection has no immediate effect because the serum finds no antibody to unite with it.

The infectious diseases differ from serum sickness in that the allergen is not introduced directly in a maximum amount, but develops gradually during the incubation period. Here again the breakdown of allergens gives rise to general symptoms. Essentially, the thesis is that the antibody-antigen reaction is a quantitative phenomenon with immunity resulting when the antibody concentration is below the level at which reaction produces clinical manifestation, and with hypersensitivity occurring when the antibody concentration is above this level.

Von Pirquet outlined his concept of allergy as follows:

#### Divisions of Allergy

- A Reactivity altered according to time (compared to a first reaction after eight to 12 days)
  - 1 Early reaction (immediate reaction) within 24 hours, obtained by intravenous injection and associated with general symptoms
  - 2 Accelerated reaction (fourth to seventh day)
- B Reactivity altered according to quantity
  - 1 Reinforced reactivity (hypersensibility, paradoxical reaction, anaphylaxis)
  - 2 Lessened reactivity (hyposensibility)
  - 3 Abolished reactivity (insensibility, immunity)
- C Reactivity altered according to quality (changes regarding color, microscopic observations)

The observations of altered reactivity and the antibody theory which resulted from these observations have led to the present-day explanation of immunity in a number of infectious diseases. In vaccinia, smallpox, and other diseases the immunity is based not on an acquired insensibility to the virus, but on antibody formation and on the early reaction. It has been shown that there exist two kinds of protection against such diseases. One is due to antibodies still existing in the body which has previously been infected. The microorganism comes immediately into contact with the antibody and is destroyed at the same time forming with the antibody a breakdown product which acts as a toxin to the surrounding tissue. Owing

to this immediate destruction, the microorganism does not develop sufficiently to give rise to general symptoms. The other kind of protection is of the type seen when a long period has elapsed between the first and the second infection. The antibodies are no longer present but the cells retain the property to form antibodies in a shorter time. The microorganism, while not immediately destroyed, does not develop to the same degree as in an animal not previously infected, and the amount of toxin produced by the interaction of antibody and microorganism is comparatively small.

It must be remembered that Von Pirquet's hypotheses were based on clinical studies and not on experimental evidence.

#### *Nature of the Antigen-Antibody Reaction* Character of Antibody

As late as 1926 antigens and antibodies were recognized only by their actions. It was not even certain that antibodies existed as material objects.

Because the phenomenon of chemical equilibrium was not completely understood, Ehrlich and others invented artificial hypotheses to explain their observations in the field of immunology. In 1926 Hartley discovered that specific precipitates contained both antigen and antibody. The antibodies proved to be proteins.

In 1931 Zinsser<sup>4</sup> wrote "It is generally assumed that antibodies cannot be separated from proteins and are usually contained in the pseudoglobulin fraction, in some cases in the euglobulin fractions of the sera."

In 1938 Heidelberger<sup>5</sup> observed the chemical nature of antibodies and concluded that they are modified serum globulins. Von Pirquet, in 1911, had maintained the same view, although without experimental evidence. It was postulated that antibodies were formed from globulin intracellularly. The molecule of globulin was thought to be synthesized in stereochemical relationship to antigen and, when released, to exhibit specific affinities for this antigen.

Breinl and Haurowitz<sup>6</sup> suggested the theory of structural complementarity of the antigen and its specific antibody—that during the process of antibody formation, antigen entered into the mixtures of amino acids and peptides and induced new groupings. Thus the formation of antibody was thought to represent the synthesis of a new kind of globulin in which the molecules arranged themselves in ways characteristic for each antigen. As the antibodies pass into the circulation, the antigen remains behind and continues to influence the formation of new antibody globulin until the antigenic component is destroyed or eliminated from the antibody-producing cell.

Pauling<sup>7</sup> advocated the concept that normal globulin and antibody globulin are essentially identical chemically but differ structurally in stereoisometric arrangement. The specific antibodies were thought to be produced "in vitro" by rearrangement of the polypeptide chains. Pauling thus assumed that all antibody molecules contain the same polypeptide chains as do the molecules of normal globulin and differ from them only in the configuration of the chains. In the formation of specific antibodies to a foreign

substance, the chain folds into a configuration which is stable in the presence of the antigen. Therefore, the animal has the ability to form specific antibodies for an unlimited number of antigens.

This theory was similar to Ehrlich's lock-and-key analogy. It replaced Cannon's theory<sup>8</sup> that an antigen acts as a template for the manufacture of a specific enzyme, which then serves as a mold for the production of antibody.

Pauling and Campbell<sup>9</sup> produced antibodies "in vitro" from normal serum globulin by denaturation and renaturation in the presence of antigen. The denaturation was accomplished by heat or by chemical action. Thus, the antigen-antibody concept emerged from the realm of hypothesis and became a biochemical fact.

*Origin of Serum Protein* It was at first suggested that serum proteins may arise from certain cells in the circulation or in the bone marrow, or from tissue cells generally.

Sabin<sup>10</sup> injected "marked antigen" (alum-precipitated dye-protein) into rabbits and saw it in macrophages. Coincident with the disappearance of the dye protein from the cells and with the appearance of antibodies in the serum, she noticed a shedding of the surface films of the macrophages without damage to the cells. She concluded "If this process of cytoplasmic shedding is a general property of globulin-producing cells, any such cell which can phagocytose antigen or allow its entrance into the cytoplasm may be a precursor of antibody. Furthermore, a part of the antibody globulin may remain within the cell for long periods of time." Landsteiner and Parker<sup>11</sup> showed that connective tissue cells can form serum proteins.

This intracellular origin of globulin might explain why an immune reaction may occur in the absence of antibodies in the blood—a point of great importance in establishing the relationship between bacterial hypersensitivity and hypersensitivity of the anaphylactic type. It may also help to explain allergic phenomena.

Thus it appears that the antibody-producing mechanism consists of a widely distributed system of cells, including macrophages, fibroblasts, and possibly even endothelial cells and to some extent epidermal cells, all of which are able to a greater or less degree to synthesize globulin. These findings placed Von Pirquet's conclusions from clinical observation on a firmer chemical basis.

*Character of Antigen* It has long been known that amino acids play a rôle in the specificity of antigens. Landsteiner first introduced the concept of "hapten"—that portion of a complex antigen which determines its serological specificity. A hapten is capable of reacting with antibodies produced by whole antigen, but is itself unable to stimulate antibody formation. Heidelberger<sup>5</sup> states "It would now seem that nearly every species of bacterium is possessed of one or more specifically reactive polysaccharides, playing a definite and often a determining rôle in bacterial specificity. These specific carbohydrates not only act as haptens but also precipitate antibody

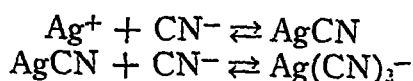
on combination with it. This may be a function of their high molecular weight." The rôle of lipoids as haptens still remains equivocal at the present time.

*Mechanism of Antigen-Antibody Interaction* It has been thought that the antigen-antibody reaction was colloidal in nature and, therefore, an adsorption phenomenon. On this basis, however, not all the observed experimental results could be explained. Recently Heidelberger<sup>9</sup> suggested that these specific interactions could be simple chemical unions following the Mass Law of inorganic chemistry. His theory is that antigen and antibody may be multivalent with respect to each other—that is, that the composition of the precipitate may vary according to the relative proportions of the reactants. In his experimental work he showed that if a small amount of type III pneumococcus polysaccharide ( $S$ ) is added to a relatively large amount of antibody ( $A$ ), antibody is precipitated by antigen in the ratio of 180:1. As increasing amounts of ( $S$ ) are added in proportion to ( $A$ ), this ratio decreases, but all of the ( $S$ ) added is precipitated, leaving ( $A$ ) in excess. Finally as increasing amounts of ( $S$ ) are added the "equivalence point" is reached, at which a slight excess of ( $S$ ) remains in solution. At this point there is also a small amount of ( $A$ ) in solution. If the amount of ( $S$ ) is increased slightly, the traces of ( $A$ ) in solution are precipitated, as greater amounts are added, however, less and less precipitate is formed until finally no precipitation occurs.

At the equivalence point, the equilibrium may be expressed by the Mass Law

$$\frac{(S)(A)}{(SA)} = K.$$

The precipitation reaction between the antigen ( $S$ ) and its antibody ( $A$ ) thus does not seem to differ in principle from a simple inorganic precipitation. A partial analogy to the inhibition zone is seen in the reaction of  $\text{AgCl}$  which is soluble in an excess of  $\text{KCN}$



Heidelberger's concept is that, as in inorganic chemistry, all the antigen-antibody reactions are reversible. The dissociation constant for each system would be different and would have to be determined experimentally.

Marrack<sup>12</sup> agrees with Heidelberger concerning the polyvalence of the antigen-antibody reaction.

Pauling, Campbell and Pressman, in 1942,<sup>13</sup> elaborated on the specific nature of the reactions between antigen molecules and antibody molecules. They pointed out that in these reactions two atoms, instead of interacting strongly with each other, as in the formation of ordinary chemical bonds, may interact weakly. "The properties of the antigen-antibody system, especially the reversibility of the complex formation, are such as to indicate that

the antigen-antibody attraction is due to these weaker interactions and not to the formation of ordinary chemical bonds." The immunological property of greatest significance is the specificity of the combining power of antibody for the immunizing agent. The forces of weak interaction between two molecules, such as the electronic van der Waals attraction, the hydrogen bond formation, and the interaction of electrically charged groups, are not specific. However, specificity can arise in the interaction of large molecules as a result of their shapes. Two large molecules may have such spatial configurations that their surfaces cannot be brought into contact except at a few isolated points. However, if two molecules possess such configurations that the surface of one conforms closely to the surface of the other, and if the electric charges are mutually attractive, they would attract each other very strongly.

These authors stated that the weight of evidence indicates that further combination of the initial antigen-antibody complexes to form a precipitate is a specific rather than a nonspecific reaction and is due to continuation of the primary combination step to form a framework structure of alternate antigen and antibody molecules.

On the basis of this physico-chemical explanation, the old distinction between chemical and physical forces has lost its meaning. It is found that the forces operative in surface phenomena are the same forces operative in chemical reactions. Therefore, the disagreement between Ehrlich and Bordet concerning chemical bond or adsorption is settled in neither's favor.

#### RELATION OF ALLERGY TO IMMUNITY

Von Pirquet was the first to point out that the antigen-antibody reaction could not only produce immunity but also cause toxic symptoms, as in serum sickness. On the basis of clinical evidence, he considered immunity to be loss of reactivity. He postulated the existence of three substances in the serum which could cause the allergic phenomena: (a) the sensitizing substance or allergen, (b) a substance which acts as a poison after reinjection (toxic substance), and (c) a substance which acts protectively and causes the phenomenon of anti-anaphylaxis or anergy. "It is *a priori* probable that (a), (b), and (c) are identical."<sup>3</sup> Rosenau and Anderson<sup>11</sup> proved the identity of (a) and (b) in guinea pigs. Doerr and Russ<sup>12</sup> stated that "the sensitizing, toxic, and anti-anaphylactic properties of the serum act quite identically on being heated and in fractional precipitation with ammonium sulfate, the sensitizing and toxic properties are both contained in the globulin fraction of the serum."

Rich<sup>10</sup> in 1941 made clinical and pathological differentiations between bacterial hypersensitivity and hypersensitivity of the anaphylactic or Arthus type. In the tuberculin or bacterial type of hypersensitivity (1) the reaction develops in hours, (2) the smooth muscles are not affected, and (3) there are no passive transfers. In the anaphylactic type, there was (1) an im-

mediate development of the local or constitutional reaction, (2) the smooth muscles are thrown into spasmodic contraction, (3) passive transfer is possible, and (4) the sensitizing antibody is found in the blood stream. There is also a difference in the mechanism of the tissue damage in the bacterial and the anaphylactic types of hypersensitivity. In the former, the local tissue damage produced by the protein is due in large part to sensitization of the individual tissue cells, in the latter, no generalized hypersensitization occurs, but vascular damage results from contact with the specific foreign protein. Rich states "The surrounding tissue damage appears to be due to interference with nutrition resulting from the vascular damage and from the clogging of the tissue spaces with hemorrhage and exudate."

Wolff-Eisner, in 1905,<sup>18</sup> was the first to suggest that clinical allergy may be related to experimental anaphylaxis. He pointed out the following fundamental similarities:

- (1) Both reactions occur in sensitive individuals
- (2) Both reactions are produced by substances with or without inherent toxicity
- (3) The degree of reaction in both cases depends upon the susceptibility of the individual and not upon the inherent toxicity or the dose of the substance
- (4) The character of the reaction is related to the susceptibility of the individual and is not a specific property of the provoking substance

The differences, as pointed out by Wolff-Eisner, are

- (1) Anaphylaxis is invariably dependent on a known previous sensitization to an antigen, usually a protein. Allergy apparently can exist without recognizable initial sensitization and can be related to non-protein substances
- (2) In anaphylaxis the sensitive state is relatively temporary. In allergy the sensitive state tends to persist throughout life
- (3) Anaphylaxis involves an antigen-antibody reaction, while allergy may or may not involve recognizable antibodies
- (4) An anaphylactic reaction may be followed by a state of complete refractoriness. An allergic reaction may be followed by only a partial desensitization

Dragstedt and Mead<sup>19</sup> injected peptone solutions intravenously into dogs and obtained reactions virtually indistinguishable from those occurring in acute anaphylactic shock. The reactions were accompanied by a liberation of histamine. In this case, no previous sensitization was necessary. The sensitivity apparently occurred spontaneously and, so far as was known, did not depend on antibodies. It seemed to last throughout life. The injection of peptone was followed by a limited degree of sensitization to the same peptone. This sensitization differed from anaphylaxis in being less regularly produced, less complete, and of a shorter duration. It showed a surprising

similarity to certain characteristics of allergic reactions listed as differentiating the latter from experimental anaphylaxis. These experiments indicated the possibility that various substances may produce directly the same kind of cellular injury and after-effect as are produced by antigen acting through antibody reactions.

Although specific antibodies cannot be demonstrated in the blood stream of patients with bacterial hypersensitivity, Rich<sup>16</sup> felt that this fact was not evidence against their rôle in the production of bacterial hypersensitivity. He held that the effective portion of the antibody is intimately associated with the cells and that there is not enough excess antibody in the circulation to permit passive transfer. The high degree of specificity of the reactions also suggested the presence of antibodies.

Dragstedt<sup>20</sup> noted that the anaphylactic reaction is characteristic for the animal rather than for the foreign substance. He believed that there is substantial evidence to show that the antibodies attached to fixed tissue cells are the ones most concerned in this reaction. He considered the delay in the development of passive sensitization following the injection of antiserum to be the time interval necessary for the antibody to become attached to the fixed tissue cells and thus render them sensitive. He noted evidences that an abundance of free antibody, instead of favoring the occurrence of an anaphylactic reaction, actually interfered with the reaction, presumably by binding the antigen before it reached the sessile receptors within the fixed tissue cells.

Kulka<sup>21</sup> studied the in vitro effects of antigen-antibody mixtures on normal living excised tissues. She placed a uterine horn in a bath containing antiserum alone or a mixture of antiserum and a small amount of antigen. The bath was drained in five minutes. Addition then of antigen in increasing amounts caused uterine contractions. Kulka concluded that the antibody had become fixed to the tissue cells and then had reacted with the antigen.

Rich<sup>16</sup> states that in bodies sensitized by injection, only the protein fraction is capable of eliciting the tuberculin type of reaction. Hypersensitivity to the polysaccharides always leads to the anaphylactic type of sensitivity. However, injection of extracted proteins into the normal body leads to only the anaphylactic or Arthus type of reaction. The conclusion drawn was that the true sensitizing antigen responsible for bacterial hypersensitivity has not yet been isolated from any bacterium.

*Rôle of Hypersensitivity in the Production of Symptoms* The symptoms produced by infections are those of a hypersensitive reaction to innocuous, non-bacterial proteins—fever, malaise, aching joints and back headache, anorexia, prostration. Rich felt that the hypersensitive state increases the degree of inflammation and the amount of tissue necrosis that a given number of bacteria or a given amount of protein will produce.

*Rôle of Hypersensitivity in Resistance to Infection* It was once thought that hypersensitivity was responsible for the increased resistance



acquired during infection. This view was based on the beliefs that (1) an accelerated and exaggerated hypersensitive reaction inhibits the spread of bacteria, and (2) hypersensitivity and acquired resistance parallel each other.

Rich<sup>16</sup> presents evidence to show that the spread of bacteria is actually accelerated rather than retarded in the hypersensitive animal and that in no case does the hypersensitive reaction protect the animal from a fatal outcome. In the immunized body, immediate immobilization of the bacteria is accomplished by the action of the antibody, which causes the bacteria to adhere to each other and to the tissues where they lodge. Immobilization has no relation to hypersensitivity. Rich was able to separate immunity from hypersensitivity by the process of passive transfer. If the serum of animals hypersensitive to and immune to pneumococci is injected intravenously into normal animals, the immunity is transferred but the hypersensitivity is not.

Cannon<sup>22</sup> agrees with Rich that antibodies can combine with the antigenic substances in the blood and influence their surface properties so that they may adhere to each other, to the phagocytes, or to the tissues. Cannon states that in the immune animal agglutination of the invader is the important early localizing phenomenon, but that phagocytosis seems to be the means by which the organisms are destroyed. "Prompt bacterial localization in immune tissue is not caused by inflammation, but is due to primary interaction between the bacteria and the immune bodies."

Culbertson<sup>23</sup> injected crystalline egg albumin into the blood stream of immunized rabbits and found that the rapid removal of albumin was accompanied by a marked decrease in the precipitin content of the blood. His experiments showed that the circulating precipitin played the predominant rôle in the elimination of crystalline egg albumin and that the fixed tissue precipitin functions "only when some of the antigen escapes union with the circulating precipitin and reaches the fixed tissues."

Opie<sup>24</sup> was of the opinion that the precipitins are very important in restricting the spread of a protein, after it has become toxic to the hypersensitive tissues, to more vital organs. The efficiency of the localizing process varies directly with the concentration of the specific precipitins in the circulating blood.

Culbertson<sup>23</sup> stated that all of the evidence obtained indicates that tissue hypersensitiveness in an actively sensitized animal is dependent upon the formation of antibody by the animal and that this is reflected by the presence of precipitin in the circulation. The tissue sensitizing substance in an anti-serum appears to be inseparable from the precipitin and is probably identical with it.

Doeri and Russ<sup>15</sup> showed the parallelism between precipitin strength of the serum and its sensitizing potentiality.

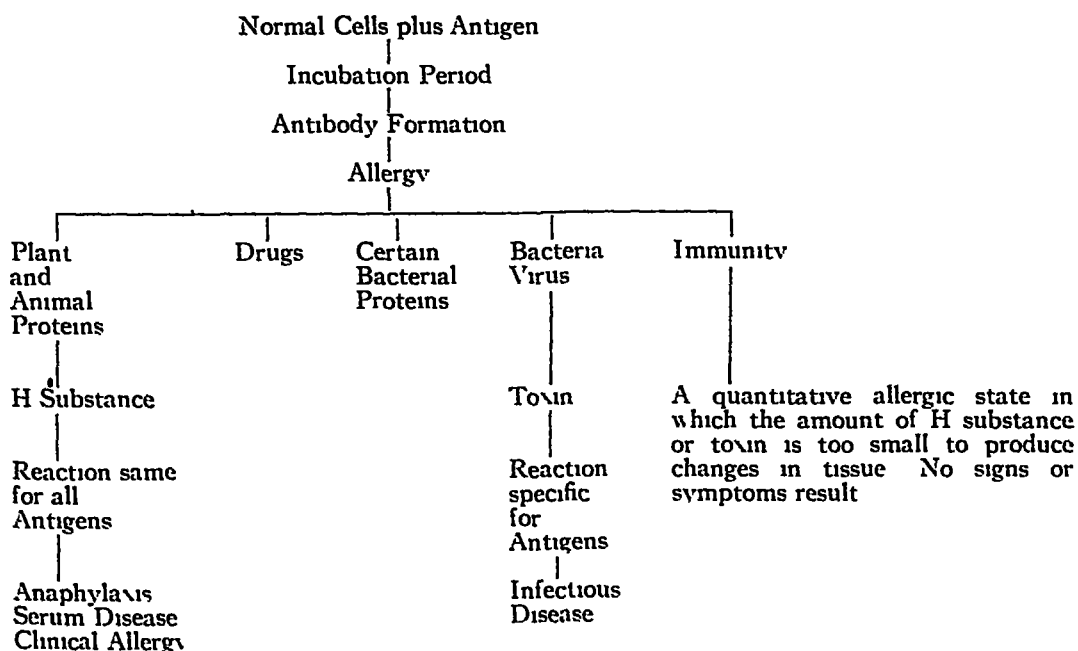
Rich<sup>16</sup> states that there is no parallelism between immunity and hypersensitivity. Immunity is somewhat inversely proportional to the intensity of the local allergic reaction.

Angevine<sup>25</sup> showed the lack of parallelism between immunity and hypersensitivity in hemolytic streptococcal infection. The intracutaneous injection of an avirulent streptococci produced a high degree of hypersensitivity with scant immunity, whereas the injection of a virulent strain produced the reverse condition.

Rich also states that there is no parallelism between the degree of hypersensitivity and the titer of protective antibodies. This theory that the antigen which stimulates the development of protective antibodies differs from that to which the body develops bacterial hypersensitivity is in agreement with the view of Von Pirquet.

According to Rich, it is possible to separate immunity from hypersensitivity by desensitization. The hypersensitivity of immunized animals wanes with time, but immunity to infection remains intact. Acquired resistance not only is independent of hypersensitivity but can actually impede the development of hypersensitivity. Yet, no one to date has produced hypersensitivity without producing immunity. Obviously, therefore, confusion still exists regarding the relationship of immunity to hypersensitivity.

Cohen in 1943<sup>26</sup> summarized this relationship from an allergist's point of view as follows:



Cohen defined immunity as a quantitative allergic state in which the amount of tissue-damaging substances formed as a result of the antigen-antibody reaction is too small to produce changes in the tissue. Thus no signs or symptoms result. Cohen postulated a latent period necessary for the development of antibodies and claimed that the tissue response was an allergic inflammation. He conceived of allergic reactions as being due to toxic materials formed as a result of the interaction of antigen, antibody, and

tissue cells According to his conceptions, the degree of reaction depends on the amount of toxic material formed, and this is determined by the quantitative relationship between antigen and antibody Since in most infections the antigen is the source of the toxic material, the histologic type of reaction is generally specific for the infecting organism, and the degree of reaction dependent on the amount of organism present from which the toxic material can be free Immunity thus is thought of as a subdivision of allergy in which the interaction of antigen and antibody releases too little toxic material to produce a reaction

The difference between allergy resulting from infections and the so-called experimental and clinical allergies lies in the nature of the toxic substance which induces the reaction In the infections, the toxic material is formed in large part from the antigen, which determines the type of local and general reaction characteristic of the specific disease In the experimental and clinical allergies, the toxic substance released by the interaction of foreign proteins with their specific antibodies is the same, no matter how dissimilar the antigens may be This fact accounts for the identity of the clinical symptoms and of the pathologic lesions The common substance formed under these circumstances could arise only from the tissues The reaction might be called "body specific" in distinction to the reactions occurring in the infections, which are "antigen specific" There is considerable evidence that the toxic substances giving rise to body-specific types of reactions are identical with the H substance described by Sir Thomas Lewis

The tissue cells are apparently not hypersensitive to ordinary amounts of the H substances or of histamine In individuals with so-called clinical allergy, they are hypersensitive only because they are exposed to a large amount of H substance produced as a result of the antigen-antibody union It is known that in passive transfer experiments normal skin reacts in an entirely comparable manner to similar amounts of H substances

Von Pirquet first postulated that the reaction of antigen and antibody formed a hypothetical toxic substance which caused clinical manifestation Many have thought that the H substance or histamine is the toxic agent released by damaged tissue cells and is the cause of the reactions

Assuming, as Dragstedt did,<sup>20</sup> that the antigen-antibody union in the anaphylactic reaction is intracellular and, as Rich did, that the same mechanism occurs in bacterial hypersensitivity, there is still no satisfactory explanation for the mechanism by which the antigen-antibody reaction produces these phenomena Numerous experiments have indicated that physiologically active substances normally present in the various tissue cells may be liberated by the injury to tissue cells caused in some unknown way by the antigen-antibody reaction

Dragstedt and Mead<sup>19,20</sup> tested the blood of anaphylactic dogs for histamine Histamine activity was found regularly whenever an appreciable anaphylactic reaction occurred By comparing the rate of disappearance of histamine activity from the blood of anaphylactic dogs to the rate of disap-

pearance of injected histamine, they were able to ascertain how much histamine was elaborated in the anaphylactic reaction. They concluded that the vascular phenomena observed in anaphylactic dogs were completely accountable by the amount of histamine released. Other investigators have confirmed this conclusion.

Tissues of sensitized guinea pigs have been shown to liberate histamine when antigen is added to the perfusion fluid, thus demonstrating the direct action of the antigen in the absence of a central, reflex, or nervous reaction.

In rabbits, it was found that blood histamine was decreased during anaphylaxis, an observation which at first seemed contradictory. It was later shown, however, that there was a shift of histamine from the corpuscular elements to the plasma. The amount of histamine thus liberated from the cells was calculated to be enough to explain the symptoms in rabbits.

There is also evidence to show that liberation of heparin and possibly choline from the tissue also occurs in anaphylaxis. The cardinal symptoms of anaphylaxis could thus be explained as being due to an autointoxication by physiologically active substances normally resident in various tissue cells and liberated from them by some change in cellular permeability brought about by the antigen-antibody reaction. Dragstedt<sup>20</sup> showed that either the fixed tissue or the blood cells could be involved.

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## HYPERSENSITIVITY AND RHEUMATIC FEVER. PART II. RELATION OF RHEUMATIC FEVER TO HYPERSENSITIVITY \*

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### CLINICAL AND PATHOLOGICAL EVIDENCES

As early as 1886 Haig-Brown observed that an incubation period precedes the development of acute rheumatism following a pharyngeal infection. This period is comparable to that which precedes the development of serum sickness following the administration of serum.

Derick, Hitchcock and Swift,<sup>27</sup> in 1928, reported that the administration of acetylsalicylic acid prevents the arthritis of serum sickness, but does not relieve the other symptoms and signs of the disease, as it does in rheumatic fever. The serum of patients treated prophylactically with this drug failed to precipitate horse serum. Untreated patients had a marked rise in precipitins in the circulation simultaneous with the occurrence of serum sickness. These observers wrote "Circulating antibodies in the serum are kept to a low

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concentration by antirheumatic drugs and the development of symptoms is inhibited." They suggested that the inhibitory action of salicylates on serum sickness may be due to their effect on the formation of antibody.

These investigators thought that the urticaria which occurs in serum sickness resulted from *active* sensitization of the skin and could not be prevented by aspirin because it does not desensitize the skin. The arthritis, on the other hand, was thought to be due to a *passive* sensitization of the joints, which did not occur until the circulating antibodies reached a high level.

In 1925 Swift<sup>28</sup> reported that the distressing arthritic symptoms of rheumatic fever are easily controlled by salicylates. Indeed, this fact has been recognized empirically since 1876. The exudative features are less prominent in patients under the full influence of salicylates than in those who do not receive the drug.

For a long time a close connection between the hemolytic streptococcus and rheumatic fever has been suspected, but the etiology of rheumatic fever is not as yet known. Swift<sup>29</sup> in 1940 suggested that the tissues of a rheumatic patient react in a peculiar manner to bacterial infection. He stated that a partial immunity to the hemolytic streptococcus would explain the fact that the microorganisms retain only a low-grade irritative capacity in the tissues, and that a reactive stage of the tissues, or hyperergy, would account for the exaggerated response to a very small stimulus.

Recently, Arnold Rich and his coworkers<sup>30, 31, 32, 33, 35</sup> have published rather convincing clinical and pathological evidence linking serum sickness, rheumatic fever and periarteritis nodosa. Reports on the pathologic picture of serum sickness were scanty until the introduction of sulfonamide therapy. Prior to this period, antisera were used chiefly against the meningococcus and the pneumococcus. The patients either died too soon to develop serum sickness or got well. With sulfonamide and serum therapy, the patient usually lives long enough to develop serum sickness.

To be sure, there had been scattered reports on serum sickness prior to the sulfonamide era. In 1929 Klinge<sup>36</sup> found that sensitization of rabbits with horse serum produced fibrinoid swelling and lesions suggestive of rheumatic fever. Clark and Kaplan,<sup>37</sup> in 1937, noted similarity between the clinical manifestations of serum sickness and those of rheumatic fever. They described endocardial, arterial and other mesenchymal lesions associated with serum disease in man and characterized by fragmentation of collagen with cellular infiltration. Since these observations had not been made in serum-treated patients who showed no clinical evidences of hypersensitivity, and since preliminary sensitization is necessary for elicitation of these lesions in animals, Clark and Kaplan suggested that these alterations represented a hyperergic reaction due to foreign serum.

Fox and Jones,<sup>38</sup> in 1944, injected rabbits with two or three large doses of horse serum intravenously or intraperitoneally. A subsequent small dose was given intravenously and the tissues were studied. Twenty of the 30

rabbits showed significant lesions, mostly in the heart, but also in the liver, lung, testis, kidney and mesentery. The cardiac lesions consisted of vascular and perivascular changes in the smaller branches of the coronary arteries. Eosinophilic infiltration of the myocardium, hyperplasia of the intima, and fibrinoid degeneration of the intima and media were present. In some instances, the lesions resembled "rheumatic arteritis." The anaphylactic symptoms had no relation to the development of the vascular lesions.

Rich<sup>30</sup> studied tissues from five patients who shortly before death had anaphylactic reactions following the injection of foreign serum. He found vascular lesions similar to those of periarteritis nodosa—necrosis, fibrinoid alteration, and hyalinization of the media of the affected arteries, together with perivascular infiltration of the entire wall with mononuclear and polymorphonuclear leukocytes. Eosinophilia was noted in some cases, and perivascular hemorrhages were seen occasionally.

There were indications that some relationship existed between the hypersensitivity reactions and the vascular lesions. Three cases showed infiltration of the myocardium with mononuclear, polymorphonuclear, and eosinophilic leukocytes, such as was first described by Clark and Kaplan.<sup>37</sup> These findings suggested that vascular lesions of this type could be the result of the anaphylactic reaction which is responsible for serum sickness.

It must be stressed that Rich<sup>30</sup> was dealing with hypersensitivity of the anaphylactic type, as opposed to the tuberculin type. Most previous studies on the relation of hypersensitivity to bacterial infections had been concerned with the tuberculin type of reaction, which is manifested in skin tests by a delayed and prolonged inflammatory reaction to the injection of specific protein of the microorganism, as contrasted with the prompt and evanescent wheal and erythema of the anaphylactic local reaction. Rich states that anaphylactic hypersensitivity to bacterial constituents may develop during infection.

Experimental evidence showed that vascular lesions of the type resulting from anaphylaxis are seen in the Arthus type of local hypersensitivity. Therefore, Rich suggested that periarteritis nodosa could be a manifestation of the anaphylactic reaction to foreign protein. Different sensitizing antigens could be responsible for the development of the vascular lesions in different persons. It was not improbable that bacterial antigens were concerned in some cases. Rich<sup>31</sup> followed his first article with a report of a case in which a biopsy specimen was taken from the scrotal sac before operation. At operation another biopsy was taken. The patient was then given sulfonamide, and seven days later had a reaction with a rise in temperature and conjunctivitis. Tissue taken from the scrotum at autopsy nine days following the hypersensitive reaction showed lesions characteristic of periarteritis nodosa, although the two previous biopsy specimens did not. This was further evidence of the rôle played by hypersensitivity in periarteritis nodosa.

Rich and Gregory<sup>32</sup> then attempted to determine the relationship of hypersensitivity and periarteritis nodosa experimentally, eliminating the complicating factor of infection and the possibility of coincidence, which were previously present. Using male albino rabbits, they injected intravenously 10 c c of sterile horse serum without preservative per kilogram of body weight. In five to eight days, nine out of 23 animals had flushing and fever, said to be a characteristic hypersensitive response in rabbits. Twelve days after the first injection of serum, all of the 23 animals were skin-tested and found to be hypersensitive. The skin reactions were of the prompt anaphylactic type. Typical Arthus reactions were observed and in some cases areas of hemorrhage and necrosis developed. When, on the seventeenth day, 1 c c of horse serum was injected intravenously, some animals died of anaphylactic shock, whereas others survived without apparent symptoms.

Histological specimens from the animals which died showed "beautiful arterial lesions typical of periarteritis nodosa." Every stage of the process was found. The simplest lesion was edema of the media which spread the muscle fibers apart. In some animals the lesions had progressed to necrosis.

This demonstration that periarteritis nodosa is a manifestation of anaphylactic hypersensitivity seemed to the investigators to be in line with the known fact that the blood vessels are susceptible to anaphylactic injury. Indeed, the anaphylactic wheal is a result of capillary damage, and the hemorrhage occurring at the site of injection in the Arthus phenomenon is clear evidence of marked vascular injury. Rich and Gregory felt it most probable that the damage to the media of the arteries seen in periarteritis results from damage to the endothelium of the intima, which is analogous to the capillary endothelial damage occurring in local anaphylactic reactions. Periarteritis could then be "hives" of the blood vessels. Rich and Gregory did not study the animals immunologically, therefore, the precipitin titers were not followed.

Smith, Zeek and McGuire,<sup>30</sup> while studying hypertension in dogs and rats, noted the occurrence of periarteritis nodosa in animals which had infection at the operative site. The lesions were not found in animals without infection.

Wilens and Sproul<sup>40</sup> found periarteritis nodosa in 10 per cent of the older experimental rats which had had frequent chronic infections.

In the course of the studies described above, Rich and Gregory<sup>33, 34</sup> noted that the lesions in the hearts of the experimental animals bore striking resemblance to those of rheumatic carditis. The characteristic cardiac lesions of rheumatic fever are (1) focal alterations in the collagen of the connective tissue, (2) the presence of Aschoff bodies, (3) focal and diffuse inflammatory lesions, (4) focal alterations in the cardiac muscle, and (5) verrucous valvular vegetations. The focal collagen alterations consist in separation of the fibers by edema, with swelling and finally degeneration of the individual fibers. These lesions were present in the hearts of the animals

which died of experimentally induced serum sickness. There were some collections of cells in the hearts of experimental animals resembling Aschoff bodies. The non-specific inflammatory lesions also were present. Focal inflammatory lesions which in many important respects were strikingly similar to those of rheumatic carditis were present in the myocardial connective tissue, the mural endocardium, and the heart valves.

Rich and Gregory<sup>33</sup> cited the following facts consistent with the view that the lesions of rheumatic fever may be due to the anaphylactic type of hypersensitivity.

*A* A fundamental manifestation of rheumatic lesions is focal injury to the connective tissue, characterized by edema and degeneration of the collagen fibrils. In local anaphylactic reactions also these alterations in connective tissue are primary and characteristic effects.

*B* During acute attacks of rheumatic fever, there often occur inflammatory necrotic arterial lesions (the so-called rheumatic arteritis) which resemble closely the vascular alterations of periarteritis nodosa. Focal or diffuse carditis sometimes occurs in association with periarteritis nodosa. Lamb<sup>35</sup> described joint pains in 39 per cent of the 40 cases of periarteritis nodosa that he reviewed. These joint pains were described as often being quite severe, "usually involving more than one joint, and behaving very much like acute rheumatic fever." Rich suggests that anaphylactic reactions may produce periarteritis nodosa in some individuals and cardiac lesions of the rheumatic type in others. The site at which anaphylactic reactions produce their effects when the sensitized body is exposed to the specific antigen seems to depend on individual predisposition. The factors governing this predisposition are still unknown today.

*C* With the more fulminant form of rheumatic fever, skin lesions of the anaphylactic type which are familiar in serum sickness (urticaria and erythema) may occur. Coburn<sup>41</sup> reported skin lesions of this type in 22.4 per cent of 162 carefully studied cases. Holt and McIntosh<sup>42</sup> write "Unless this occurs as a manifestation of serum disease, it is nearly always rheumatic in origin."

*D* Purpura is a recognized manifestation of acute rheumatic fever, it is also a recognized manifestation of anaphylactic hypersensitivity, occurring occasionally during serum sickness.

*E* Tissue eosinophilia, a hall-mark of local anaphylactic conditions, appears to be more frequent in acute rheumatic carditis than is ordinarily appreciated. It is found only in very active acute cases or in acute exacerbations of chronic cases. The eosinophiles disappear from the tissue long before Aschoff bodies are formed.

*F* Acute rheumatic fever and the anaphylactic reaction of serum sickness have the following features in common: (1) fever, (2) arterial lesions of the type occurring in periarteritis nodosa, (3) anaphylactic cutaneous lesions, (4) arthritis, (5) similar cardiac lesions. Patients with serum sickness rarely die, for this reason, there are very few reports on the



pathologic lesions of the heart in such cases. There are scattered reports in the literature indicating that serum sickness may cause both organic and functional cardiac damage. Some observers have reported the development of cardiac arrhythmia during serum sickness and a muffled first sound comparable to that which one may observe during the course of acute articular rheumatism.

G. The focal character of Aschoff bodies is not inconsistent with a generalized anaphylactic hypersensitivity. Urticaria and periarteritis nodosa are both focal lesions.

H. Boots and Swift<sup>48</sup> showed that the synovial exudate resulting from the arthritis of serum sickness is microscopically indistinguishable from that occurring in the joints of patients with rheumatic fever.

I. Transient paresis is well known to occur during chorea associated with rheumatic fever. Transient paresis developing during serum sickness has also been reported in the literature. The paresis is thought to be due to vascular changes.

J. Finally, the anaphylactic arthralgia of serum sickness is relieved by salicylate.

In a later communication Rich and Gregory<sup>35</sup> reported that the pulmonary lesions of rheumatic fever are basically identical with those resulting from anaphylactic hypersensitivity. Peculiar pulmonary lesions associated with some cases of rheumatic fever had previously been described. The primary alteration was focal damage of the alveolar capillaries. In their mildest form, the lesions were manifested only as exudates of fluid into the adjacent alveolar spaces with some leukocytic infiltration. In more severe cases focal necrosis of the capillary endothelium occurred. Other writers had described the same peculiar focal pulmonary lesions in patients under treatment with sulfathiazole, these were shown to be due to hypersensitivity.

Histologic comparison of the lesions resulting from the two causes revealed them to be basically identical. The explanation advanced was that areas of pulmonary edema which resulted from the pulmonary congestion were present in the rheumatic cases, permitting the passage of antigen and antibody through the pulmonary capillary endothelium and thus providing an opportunity for anaphylactic reaction to occur in the lung. This capillary damage, varying from increased permeability without exudation of fluid to necrosis of the endothelium, hemorrhage, or thrombosis, is the characteristic local anaphylactic effect which occurs wherever the sensitizing antigen and its antibody meet in vascular tissues. Rich and Gregory concluded that rheumatic pneumonitis is merely the result of focal anaphylactic capillary damage to the lung. It may represent the pulmonary analogue of the urticaria, erythema, and purpura which occur in rheumatic fever and in a wide variety of anaphylactic conditions.

Lichtwitz,<sup>11</sup> in his recent monograph on rheumatic fever, states that "rheumatic fever is a non-infectious disease. It is not caused by a specific

microorganism or virus, but by a sensitization to antigens, protein in nature, which in most cases are products of microorganisms. These microorganisms may be either pathogenic or non-pathogenic. But the clinical similarity of serum sickness to a certain type of rheumatic fever would seem to indicate that such sensitizing antigens may also arise in response to foreign proteins that are not of microbic origin."

Lichtwitz states that rheumatic fever strikes at tissues of mesenchymal origin, but that the entire mesenchyme is rarely affected. "Characteristically, the morbid agent selects for its attack the fibrous tissue and vascular system of an organ such as the heart or a number of structures of the same kind. The reason why certain organs or structures are commonly attacked, while others are usually spared or protected, is not yet understood."

"No matter where the rheumatic lesion occurs, fundamentally its nature is the same. It starts with a swelling of the base substance of the connective tissue. This swelling may clear up or the process may go on to produce degenerative changes. At first, the degeneration is 'fibrinoid' in character, later, as it progresses, wax-like, strongly refractory masses appear. At this stage, reversibility is no longer possible. These necrotic masses may persist, or the defense mechanism mobilizes, surrounding and walling off these masses, stimulating the proliferation of the fixed tissue cells and producing giant cells. In other words, there is an inflammatory reaction against the necrotizing factor and its effect."

"A striking fact about the structural changes in rheumatic fever is their tendency to bilateral symmetry. This bilateral symmetry indicates that the central nervous system influences the development of the rheumatic lesion."

"Microorganisms produce specific proteins called antigens, which stimulate the cells of the invaded host to mobilize for defense. Until the defense is adequate, the invasion advances, and the disease rages. When the defense grows strong enough to overcome the invasion, the disease subsides and immunization and healing occur. Especially if the struggle is protracted, the victim is apt to become abnormally sensitized to the antigen of the invader. In such a case, the acute disease of invasion tends to become the chronic disease of defense." Lichtwitz feels that the immune reaction is preceded by a phase of increased sensitivity.

Susceptibility, immunity and sensitization all depend especially upon the activities of the cells of the reticulo-endothelial system. In the malaria of birds, the cells of this system seem to increase in number, to develop greater phagocytic activity, and to change their specific response to antigens. When this change results in a lowered sensibility to the antigen, an active immunity has been attained.

Under antigen stimulation the receptors multiply. If more are produced than the cell requires, the surplus receptors make their way into the blood, where they act as specific antibodies, endowing the serum with the

power to confer passive immunity, which may be measured in terms of precipitins, agglutinins, and analogous substances

"By some such process both humoral and cellular immunity normally develop. However, the development may miscarry in two ways: (1) the cell may fail to sever its vital connection with the antigen-occupied receptors, and (2) the cell may fail to cast off the surplus receptors, and they may remain as integral and abnormally specialized units of the protoplasm of the affected cell. When the immunizing process thus miscarries, the susceptibility of the cell to the antigen and the potency of the antigen's effect on the cell may be dangerously enhanced."<sup>44</sup>

The reproduction and release of specific receptors, together with the cell's failure to sever its vital connection with the antigen-occupied receptors, result in free antibodies in the blood, with a corresponding degree of humoral immunity occurring simultaneously with cellular sensitization. The titer of immune bodies such as precipitins and agglutinins is not a constant index of the activity of a disease, evidently it is the cellular rather than the humoral immunity which is of primary importance. There is no way today of analyzing the processes of cellular immunity. Lichtwitz<sup>44</sup> states: "Allergic sensitization is immunization arrested at a dangerous stage of imperfection. No matter what their biochemical mechanism may actually be, sensitization and immunization are unquestionably cellular function."

#### IMMUNOLOGICAL EVIDENCES

In 1903 Hamburger and Moro<sup>45</sup> noted the formation of precipitin following the injection of horse serum into human beings and suggested the relation between the development of serum sickness and the appearance of precipitins in the circulation. Francioni<sup>46</sup> in 1908 noted that serum sickness in men is accompanied by a diminution in the circulating complement.

Mackenzie and Leake,<sup>47</sup> in 1921, studied the time relation involved in the disappearance of the precipitinogen, the appearance of the precipitin, and the development of serum sickness. They showed that the onset of symptoms is accompanied by the appearance of circulating precipitin (antibody), and the subsidence of symptoms by the disappearance of precipitin from the blood stream. In patients who fail to develop serum sickness, the precipitinogens in the circulation persist and precipitin does not appear. These observations supported the concept that serum disease is an antigen-antibody reaction. These two investigators found marked individual variations in reactions to the administration of foreign serum. They explained the reactions described above as follows: The foreign serum unites with the tissue cells, causing the production of antibodies. Intracellular union of antigen and antibody gives rise to symptoms. After a while, the antibodies are produced in excess and cease to be intracellular. Therefore, for a time, both antigen and antibody are in circulation. The good precipitin formers have the severe serum reactions.

Karelitz and Glorig<sup>48</sup> produced passive sensitization with the antibody to horse serum contained in the serum of patients convalescing from serum sickness

Perry,<sup>49</sup> in 1939, noted the suppression of rheumatic fever by salicylates and associated this with their effect on antibody. Boisvert<sup>50</sup> found that in rheumatic children a high antistreptolysin titer persisted over an unusually long period, and suggested that there was a stimulus for antibody production in rheumatic fever

Coburn and Pauli<sup>52</sup> studied epidemic infections by pathogenic agents in a well controlled group of 30 rheumatic subjects. Many of the children carried a strain of hemolytic streptococcus in the throat flora, but the organism produced no detectable toxin and was not associated with respiratory disease. Four patients had chicken pox during the winter months. None developed rheumatic recrudescences, and the antistreptolysin titer remained constant. During a severe epidemic of influenza, all but six of the children were ill with the disease. The filtrable virus responsible for the outbreak was recovered. This agent, however, did not activate the rheumatic process. Those children who had influenza alone had no rise in the antistreptolysin titer. Two of the patients with coincident influenza and hemolytic streptococcal pharyngitis developed fulminating rheumatic attacks, and one of them died. The clinical manifestations developed simultaneously with a sharp rise in antistreptolysin titer.

The influenza epidemic was followed within a month by a wholesale infection with a strain of hemolytic streptococcus which was culturally, biochemically, and serologically different from that of the carrier strain and was found to be a good skin toxin producer. Of the 17 rheumatic individuals infected with this strain of streptococcus, 14 developed acute rheumatism. In these 14 cases, there was a rise in the antistreptolysin titer coincident with the onset of rheumatic symptoms. Four of these patients had not been involved in the influenza epidemic.

Coburn<sup>54</sup> claims that there are three distinct clinical phases in the evolution of the rheumatic attack:

- 1 Acute respiratory infection (usually lasting not more than three days)
- 2 Afebrile asymptomatic period (14 days)
- 3 Phase of acute rheumatism (one or more cycles of activity lasting 10 to 14 days and separated by periods of remission lasting seven to 10 days)

Coburn felt that phase two was crucial in the genesis of the rheumatic activity. The only abnormality found in this symptom-free period was a diminution of serum complement. The level returned to normal with recovery from rheumatic fever. Decreases in serum complement are known to occur when there are present in the circulation both an antigen and its antibody, with the former in excess. If antigen be present in excess, then its

antibody should be present in excess shortly after return of the complement to normal. This could possibly occur in phase three. Coburn and Pauli showed experimentally that precipitation occurs only between phase two serum (presumably containing an excess of antigen) and phase three serum (presumably containing an excess of antibody). It was thought that the antigen was not present with the acute pharyngitis but developed in phase two. A precipitin was found in phase three serum which reacted with antigen present in homologous serum just before the onset of the attack. The antigen concentration was maximal just before the onset of the rheumatic symptoms and disappeared within three days thereafter. Precipitin appeared during the peak of the rheumatic cycle and disappeared with its subsidence. The most intense reaction occurred between phase two and phase three sera from the severest cases.

In uncomplicated streptococcal infections without rheumatism, no precipitin reactions occurred. In patients who had had a polycyclic course, serum taken at the height of the second cycle contained good precipitin for phase two antigen. The precipitin disappeared from the serum during periods of remission between the cycles of activity. Serum taken during the remissions was tested with serum taken during the second cycle and known to contain antibodies. Precipitation occurred, showing the presence of antigen during the remissions. Phase two antigen and remission antigen were shown to be identical as to reactivity.

Coburn and Pauli<sup>54</sup> also noted that cross reactions between patients are possible, that is, that the reactions are not patient-specific but will occur between the sera of any two rheumatic patients, provided such sera represent appropriate stages of the disease. The investigators then showed that the precipitin reaction is disease-specific. It does not occur when either the antigen or the antibody is replaced by serum from patients with other acute febrile diseases. They noted that neither the fever nor the rapid sedimentation rate in rheumatic fever paralleled the occurrence of the precipitin reaction.

### RÔLE OF SALICYLATES IN RHEUMATIC FEVER

Swift,<sup>55</sup> in 1922, experimentally studied the effect of salicyl on the streptococcal immune bodies. He determined the effect of daily doses of sodium salicylate by mouth on the development of immunity in rabbits which had received intravenous injections of *Streptococcus viridans*. Some of these injections contained living organisms, others were in the form of vaccines. Washed sheep red cells were used in the control experiment. As compared with the control animals, the salicylate-treated rabbits showed a depression of agglutinin, hemolysin, and complement-fixing antibodies. The intravenous injection of antigen previously treated in vitro with sodium salicylate resulted in a lower antibody curve than that seen in the rabbits receiving untreated antigen intravenously and salicylates by mouth. The depressant

action of sodium salicylate on antibody formation was felt to be due partly to some direct action on the antigen and partly perhaps to a decreased absorption rate in the salicylized animals. Swift suggested that the beneficial effects of salicylates in rheumatic fever probably could not be attributed to an increased production of circulating immune bodies. This view is compatible with the present idea that salicylates tend to suppress excess antibody formation.

Hanzlik<sup>76</sup> noted that salicylates were bound to some extent by the blood proteins, the degree varying with the condition of the body.

Derick, Hitchcock, and Swift<sup>27</sup> in 1928 noted that the serum of patients treated prophylactically with acetylsalicylic acid failed to precipitate horse serum.

Coburn and Moore<sup>57</sup> reported that the administration of salicylate to rheumatic subjects during respiratory infections with hemolytic streptococcus and for two weeks after such infections prevented the development of the rheumatic attack or suppressed it below the clinical level. Of 47 young rheumatic subjects who received prophylactic doses of sodium salicylate, only one had rheumatic fever following an attack of hemolytic streptococcus pharyngitis. Of 139 untreated cases, 82 escaped and 57 developed rheumatic fever. These statistics prove that the failure of rheumatic subjects to develop attacks following streptococcal pharyngitis was related to the salicylate prophylaxis.

Coburn and Kapp<sup>78</sup> studied the *in vitro* effect of salicylates on the precipitation of antigen with antibody. Sodium salicylate added to a system containing crystalline egg albumin and its antibody inhibited the formation of precipitate, the degree of inhibition being related to the concentration of salicylate and to the antigen-antibody ratio. The immune system became progressively less sensitive to the action of salicylate as the excess of antibody became larger. Formed precipitate was partly dissolved when it was resuspended in the presence of salicylate. The salicylate effect on the immune precipitate was reversible. The action of salicylates *in vivo* is not known to date.

On the basis of this experimental evidence, Coburn<sup>58</sup> treated rheumatic subjects with large doses of salicylates. It must be remembered that salicylates do not alter the capacity of the bacterial agent to elaborate antigen. Moreover, they exert no action on the infectious agent. It was hoped, however, that alteration of the abnormal antibody response would decrease the severity of the inflammation of the vascular tissue, thus preventing disabling heart disease.

Coburn mentioned the recent work of Lutwak-Mann,<sup>60</sup> who found that salicylates depressed the respiration of the liver and the kidney cortex in rats. "Proof that profound changes in metabolism are provoked by the injection of salicylate is provided by the change in the composition of the reducing substance in the tissues. The disappearance soon after salicylate injection

of nearly all the liver glycogen and its full restoration 24 hours later clearly indicates an effect on several as yet unidentified enzymic processes" <sup>60</sup>

Abbassy, Hill, and Harris <sup>61</sup> found that following the administration of large doses of ascorbic acid, patients with rheumatic arthritis excreted much less of the acid than did normal subjects. It is possible that in rheumatic disease, the metabolism of the reducing substance is affected in some hitherto unknown way, and that the beneficial effect of salicylate may be linked with its ability to influence this phase of metabolism.

### IMMUNIZATION AGAINST RHEUMATIC FEVER

Many investigators have accepted the rôle of hypersensitivity in rheumatic fever and have attempted to approach the problem by rendering the susceptible individuals hyposensitive. Swift, Hitchcock, Derick and McEwen, <sup>62</sup> in the hope of accelerating the immunizing process in rheumatic subjects, gave them intravenous injections of a heat-killed culture of hemolytic streptococci, streptococcal nucleoprotein, and a mixture of pulverized streptococci. The strain Q33 used for the preparation of the vaccine was isolated from the tonsillar exudate of a patient who had suffered for months from severe polyarthritis and carditis. Their reasoning was based on experimental work showing that intravenous injection into hypersensitive rabbits changed their reactivity to an immune hyposensitivity. In their small series of patients, however, the results were inconclusive. These investigators stated that the "failure of a fair proportion of the patients to react favorably to the immunization with a single strain suggests that this immunizing strain is too far removed from the sensitizing strain antigenically."

Wilson and Swift <sup>63</sup> used an intravenous vaccine made from a heat-killed culture of hemolytic streptococci of the same Q33 strain in 0.5 per cent phenol and gave nine to 12 weekly injections in 1 c.c. doses of varying concentrations to 172 children. Systemic reactions were infrequent. No focal reactions were observed. Forty-five per cent of the treated children, as compared with 18 per cent of the controls, were free from recurrences for 16 months to two years after the treatment. Examination of the serum of 56 treated children did not reveal agglutinins or precipitins. The authors thought this negative finding of no importance, "for active immunity has been observed in the absence of demonstrable circulating antibodies. The assumption that the lowered incidence of recurrence observed in the vaccinated group was due to a diminished susceptibility resulting from a change in reactivity of the tissues may be explained by the conception of the disease as an allergic (hyperergic) phenomenon."

Wasson and Brown <sup>64</sup> attempted to immunize children with known rheumatic fever by frequent subcutaneous injections of a crude toxin preparation made from the N.Y. 5 strain of hemolytic streptococcus. The disadvantages of the crude toxin were that up to 38 visits to the clinic were necessary, the

group treated was limited, and the local reactions were frequent and severe. General reactions occurred occasionally.

Because of these disadvantages, Wasson and Brown next used a tannic-acid-precipitated toxin of the N Y 5 strain of hemolytic streptococcus, which was used by Veldee of the U S Public Health Service against scarlet fever. They gave 35,000 skin-test doses of attenuated toxin intradermally in four injections three weeks apart. The largest dose was repeated semi-annually, beginning six months after the fourth injection.

The study was started in September, 1940. Forty-two patients with rheumatic carditis were given the toxin and 32 were used as controls. Of the treated group, a few patients had subacute rheumatic symptoms, but not a single one had an attack of rheumatic fever. In the control group, there were 11 attacks of acute rheumatic fever with three deaths.

In September, 1941, another group of 38 patients was treated. There was one possible attack of rheumatic fever in this group during the ensuing winter, as compared with six attacks in the control group of 29 patients.

The authors stated "The end results appear good in conferring what may prove a lasting immunity against acute rheumatic infections."

### DISCUSSION

A review of the evolution of the concept of hypersensitivity shows that the early workers in the period from 1900 to 1910 described all the phenomena involved and advanced hypothetical explanations which have been substantiated by subsequent experiments. Richet<sup>2</sup> must have suspected some relationship between immunity and hypersensitivity, but postulated the existence of two separate substances to explain the two phenomena. Von Pirquet,<sup>3</sup> in his shrewd clinical analyses, described the different types of allergic responses. Moreover, he extended the concept of hypersensitivity and applied it to infectious diseases. He was the first to show the deleterious effects of antigen-antibody reactions as well as their usefulness in the internal environment. He conceived of immunity as a phase in the quantitative relationship of antigen to antibody during which the antibody concentration is below the level of clinical manifestation. The recent biochemical analyses of this reaction seem to substantiate his views.

Within the last few years the nature of the antigen-antibody reaction has been firmly established on an experimental biochemical basis. Study of organic reactions in the light of physical chemistry by Heidelberger,<sup>5</sup> Pauling and Campbell,<sup>6</sup> and others have shown no essential difference in the mechanisms of organic and inorganic reactions. The origin of antibody, the mechanism of its formation, the character of the antigen, and the mechanism of antigen-antibody interaction have been somewhat clarified, but are still by no means completely understood. One sees the trend toward quantitative evaluation of the previously clinical and qualitative concepts.

The question of the relationship between immunity and allergy remains



unsolved The relationship between bacterial hypersensitivity and hypersensitivity of the Arthus type also is not clear Rich<sup>16</sup> differentiated clearly between the two on clinical and pathological grounds His later work, showing rheumatic fever to be hypersensitivity of the Arthus or anaphylactic type, stresses this difference It is debatable whether bacterial hypersensitivity is also an antigen-antibody reaction Perhaps our analytical methods are still too crude to demonstrate the minute quantities of antigen necessary to evoke the allergic response To date, we have no satisfactory means of studying intracellular metabolism Dragstedt and Mead<sup>10</sup> have presented experimental evidences linking the two types of hypersensitive reactions No definite conclusions seem to be warranted at the present

Some investigators regard the allergic response as an integral part of the body's defense mechanism, whereas others, such as Rich,<sup>16</sup> regard it as being deleterious Rich believes that there is no parallelism between immunity and hypersensitivity and, in fact, holds that immunity is somewhat inversely proportional to the intensity of the local allergic reaction He postulated the existence of two different antigens for immunity and hypersensitivity These have not been demonstrated to date

The rôle of the circulating antibodies and their relation to immunity and hypersensitivity are not clear Different authors have demonstrated precipitins in both immune and hypersensitive animals The rôle of the fixed tissue in the production of immunity or hypersensitivity also is not clear

Cohen<sup>26</sup> saw no fundamental difference between the allergic reaction and immunity Immunity to him meant a quantitative allergic state in which the toxic substance released by the antigen-antibody reaction was insufficient to produce tissue changes This unitarian concept may prove to be more valuable in the final explanation of the allergy-immunity relationship than the postulate of multiple antibodies Further quantitative studies should prove or disprove its validity The alternative theory is that there are multiple stereoisometric variations of the serum globulin formed in the antigen-antibody reaction It would be a tremendous task to isolate these variants

That the antigen-antibody reaction occurs both *in vivo* and *in vitro* is known, but the pathological physiology whereby the tissue cells are damaged during an allergic response is not known with certainty It is known that histamine and probably other substances normally present in the body are involved in some way quantitatively, but the exact mechanism of action is not known These physiologically active substances may or may not be the "toxic substances" implicated in antigen-antibody reactions

The therapeutic response to salicylates in both serum sickness and rheumatic fever points toward some relationship between the two diseases The studies of Clark and Kaplan<sup>37</sup> and of Rich<sup>31, 32, 33, 34, 35</sup> on the pathology of serum sickness and rheumatic fever respectively show similar basic lesions Assuming that serum sickness is an anaphylactic reaction, one can conclude that the lesions of rheumatic fever resemble those of anaphylaxis Whether

anaphylactic reactions have ever been produced by bacterial infections is not definitely known. However, if Dragstedt's work<sup>17, 19, 20</sup> is valid, there is perhaps a closer relationship between bacterial hypersensitivity and anaphylactic hypersensitivity than is generally conceded. Rich presents rather convincing evidence that the lesions and the clinical picture in rheumatic fever resemble those of serum sickness and other anaphylactic reactions.

Lichtwitz<sup>44</sup> states that rheumatic fever is due to an antigen-antibody reaction, but also says that the sensitization in rheumatic fever may be due to any type of antigen. Once the rheumatic state is established, Lichtwitz feels that any stimulus, such as exposure to cold, may cause a flare-up. This theory differs from the more limited view of most investigators, who attribute rheumatic fever to a sensitization of the body to the streptococcus or its product. Although the series of cases studied by Coburn and Pauli<sup>51, 52, 73, 54</sup> was small and probably not statistically significant, one gains the impression that only a particular strain of streptococcus causes flare-ups of clinical rheumatic fever. Their observations that such flare-ups had no relation to other infections would invalidate Lichtwitz's claim that the antigen-antibody system involved may be due to many varied stimuli. The evidence tends to show that in rheumatic fever the body is sensitized to a streptococcus or its product.

Although the immunological relationships of precipitins in immunity and hypersensitivity is not firmly established, Mackenzie and Leake<sup>47</sup> noted a direct relationship between the appearance of precipitin and the onset of serum sickness. Coburn<sup>41</sup> likewise observed the appearance of precipitin at the height of the rheumatic cycle and its disappearance with the subsidence of rheumatic activity. The greatest *in vitro* precipitation reaction occurred in the sera of patients with the most severe clinical symptoms. Coburn and Pauli<sup>54</sup> then showed that the reaction was not patient specific.

Coburn and his coworkers later showed that the antigen-antibody reaction *in vitro* is altered by the action of salicylates on the antibody, and that the extent of this reaction was reversible. By the administration of prophylactic doses of salicylates to rheumatic subjects Coburn and Moore<sup>57</sup> showed that the rheumatic process is inhibited by salicylate. Thus, it can be stated on good experimental evidence that rheumatic fever is an anaphylactic type of response to some strains of the streptococcus or to their products. It is an antigen-antibody reaction. This reaction may be effectively blocked prophylactically or therapeutically by salicylates which act on the antibody through some yet unknown mechanism.

That the tissue cell damage resulting from the antigen-antibody reaction may involve enzymatic systems is suggested by the recent work of Lutwak-Mann<sup>60</sup> and others.

Swift and his coworkers<sup>62, 63</sup> have reasoned that if rheumatic fever is a hypersensitive reaction it should be possible to render rheumatic individuals hyposensitive. Their method of approach by intravenous vaccination yielded

unconvincing results Wasson and Brown,<sup>61</sup> giving repeated subcutaneous injections of tannic-acid-precipitated toxin of the hemolytic streptococcus, obtained remarkably good results of 80 patients treated, only one had a suspected exacerbation of rheumatic fever Time alone can tell whether this desensitization procedure will confer a lasting immunity If so, it will replace salicylate therapy and prophylaxis and will control the ravages of rheumatic fever

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### BIBLIOGRAPHY

- 1 RATNER, B The evolution of our present knowledge of hypersensitiveness, *Bull New York Acad Med*, 1942, xviii, 527-536
- 2 RICHT, C R Anaphylaxis, tr by J Murray Bligh, 1913, London, Constable
- 3 VON PIRQUET, C E Allergy, *Arch Int Med*, 1911, vii, 258-288, 383-436
- 4 ZINSSER, H Resistance to infectious diseases, ed 4, 1931, Macmillan, N Y
- 5 HEIDELBERGER, M Contributions of chemistry to the knowledge of immune processes, *Medicine*, 1933, xii, 279-295
- 6 BREINL, F, and HAUROWITZ, F Chemische Untersuchung des Präzipitates aus Hamoglobin und Anti-Hamoglobin-Serum und Bemerkungen über die Natur der Antikörper, *Ztschr f physiol Chem*, 1930, cxcii, 45-57
- 7 PAULING, L Theory of structure and process of formation of antibodies, *Jr Am Chem Soc*, 1940, lxii, 2643-2657
- 8 CANNON, P R Antibody production and the anamnestic reaction, *Jr Lab and Clin Med*, 1942, xxviii, 127-139
- 9 PAULING, L, and CAMPBELL, D H The manufacture of antibodies in vitro, *Jr Exper Med*, 1942, lxxvi, 211-220
- 10 SABIN, F R Cellular reactions to dye-protein with a concept of mechanism of antibody formation, *Jr Exper Med*, 1939, lxx, 67-82
- 11 LANDSTEINER, K, and PARKER, R C Serological tests for homologous serum proteins in tissue cultures maintained on foreign medium, *Jr Exper Med*, 1940, lxxi, 231-236
- 12 MARRACK, J R Immunochemistry, *Ann Rev Biochem*, 1942, xi, 629-658
- 13 PAULING, L, CAMPBELL, D H, and PRESSMAN, D The nature of the forces between antigen and antibody and of the precipitation reaction, *Physiol Rev*, 1943, xxiii, 203-219
- 14 ROSENAU, M, and ANDERSON, J F *Bull 29, Hyg Lab U S P H and M H S*, 1906
- 15 DOERR, R, and RUSS, V K Studien ueber Anaphylaxie Die Identitat der anaphylaktisierenden und der toxischen Substanz artfremder Sera, *Ztschr f Immunitatsforsch u exper Therap*, 1909, ii, 109
- 16 RICH, A R Significance of hypersensitivity in infections, *Physiol Rev*, 1941, xxi, 70-111
- 17 DRAGSTEDT, C A Anaphylaxis and allergy, *Ann Int Med*, 1939, xiii, 248-254
- 18 WOLFF-EISNER, H Clinical immunity and serodiagnosis, *Transl 1911, Bailliere, Tindall and Co*, London
- 19 DRAGSTEDT, C A, and MEAD, F B Peptone shock, *Jr Pharmacol and Exper Therap*, 1937, li, 429-436
- 20 DRAGSTEDT, C A Anaphylaxis, *Physiol Rev*, 1941, xxi, 563-587
- 21 KULKA, A M Studies on antibody-antigen mixtures, the effect on normal living excised tissue and its dependence on the presence of free antibody in the mixture, *Jr Immunol*, 1943, xli, 235-238

- 22 CANNON, P R Functional significance of specific agglutinins and precipitins, *Physiol Rev*, 1940, xx, 89-114
- 23 CULBERTSON, J T Rôle of precipitin antibody in removal of intravenously injected antigen, *Jr Immunol*, 1935, xxviii, 279-295
- 24 OPIE, E L Desensitization to local action of antigen (Arthus phenomenon), *Jr Immunol*, 1924, ix, 247-253
- 25 ANGEVINE, D M Fate of virulent hemolytic streptococcus injected into skin of normal and immunized rabbits, *Jr Exper Med*, 1936, lxi, 131-147
- 26 COHEN, M B Basic relationship of allergy and immunity, *Jr Allergy*, 1943, xiv, 116-120
- 27 DERICK, C L, HITCHCOCK, C H, and SWIFT, H F The effect of anti-rheumatic drugs on the arthritis and immune body production in serum disease, *Jr Clin Invest*, 1928, v, 427-440
- 28 SWIFT, H F Rheumatic fever, *Am Jr Med Sci*, 1925, clxx, 631-647
- 29 SWIFT, H F Rheumatic heart disease Pathogenesis and etiology in their relation to therapy and prophylaxis, *Medicine*, 1940, xix, 417-440
- 30 RICH, A R Rôle of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy, *Bull Johns Hopkins Hosp*, 1942, lxxxi, 123-140
- 31 RICH, A R Additional evidences of rôle of hypersensitivity in etiology of periarteritis nodosa, another case associated with sulfonamide reaction, *Bull Johns Hopkins Hosp*, 1942, lxxxi, 375-379
- 32 RICH, A R, and GREGORY, J E The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, *Bull Johns Hopkins Hosp*, 1943, lxxiii, 65-88
- 33 RICH, A R, and GREGORY, J E Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity, *Bull Johns Hopkins Hosp*, 1943, lxxiii, 239-264
- 34 RICH, A R, and GREGORY, J E Further experimental cardiac lesions of rheumatic type produced by anaphylactic hypersensitivity, *Bull Johns Hopkins Hosp*, 1944, lxxv, 115-134
- 35 RICH, A R, and GREGORY, J E On anaphylactic nature of rheumatic pneumonitis, *Bull Johns Hopkins Hosp*, 1943, lxxiii, 465-478
- 36 KLINGE, F Die Eiweissüberempfindlichkeit (Gewebeanaphylaxie) der Gelenke Experimentelle pathologisch-anatomische Studie zur Pathogenese des Gelenkrheumatismus, *Beitr z path Anat u z allg Path*, 1929, lxxxi, 185-216
- 37 CLARK, E, and KAPLAN, B I Endocardial, arterial, and other mesenchymal alterations associated with serum disease in man, *Arch Path*, 1937, xlv, 458-475
- 38 FOX, R A, and JONES, L R Vascular pathology in rabbits following administration of foreign proteins, *Proc Soc Exper. Biol and Med*, 1944, lv, 294-295
- 39 SMITH, C C, ZEEK, P M, and MCGUIRE, J Periarteritis nodosa in experimental hypertensive rats and dogs, *Am Jr Path*, 1944, x, 721-735
- 40 WILENS, S L, and SPROUL, E E Spontaneous cardiovascular disease in rat II Lesions of the vascular system, *Am Jr Path*, 1938, xiv, 201-216
- 41 COBURN, A F The factor of infection in the rheumatic state, 1931, Williams & Wilkins Co, Baltimore
- 42 HOLT, L E, and MCINTOSH, R Diseases of infancy and childhood, 1940, Appleton-Century Co, New York, p 1193
- 43 BOOTS, R H, and SWIFT, H F Arthritis of serum sickness, *Jr Am Med Assoc*, 1923, lxxv, 12-15
- 44 LICHTWITZ, L Pathology and therapy of rheumatic fever, 1944, Grune and Stratton, New York

- 45 HAMBURGER, F, and MORO, E Über die biologisch nachweisbaren Veränderungen des menschlichen Blutes nach der Seruminjektion, Wien klin Wchnschr, 1903, xvi, 445-447
- 46 FRANCONI, C La diminuzione del complemento nella malattia da siero, Riv clin pediat, 1908, vi, 321-330
- 47 MACKENZIE, G M, and LEAKE, W H Relation of antibody and antigen to serum disease susceptibility, Jr Exper Med, 1921, xxxiii, 601-620
- 48 KARELITZ, S, and GLORIG, G Studies on the specific mechanism of serum sickness III Passive sensitization with antibody contained in serum sickness convalescent serum, Jr Immunol, 1943, xlvii, 121-131
- 49 PERRY, C B Relationship between acute rheumatism and streptococcal antifibrinolysin, Arch Dis Child, 1939, xiv, 32-39
- 50 BOISVERT, P L Streptococcal antifibrinolysin test in clinical use, Jr Clin Invest, 1940, xix, 65-74
- 51 COBURN, A F, and PAULI, R H Significance of prolonged streptococcal antibody development in rheumatic fever, Jr Clin Invest, 1939, xviii, 141-145
- 52 COBURN, A F, and PAULI, R H Studies on the immune response of rheumatic subject and its relationship to the activity of the rheumatic process, observations on an epidemic of influenza followed by hemolytic streptococcus infections in a rheumatic colony, Jr Exper Med, 1935, lxii, 137-158
- 53 COBURN, A F, and PAULI, R H Studies of the relationship of *Streptococcus hemolyticus* to the rheumatic process, observations on the immunological responses of rheumatic subjects to hemolytic streptococcus, Jr Exper Med, 1932, lvi, 651-675
- 54 COBURN, A F, and PAULI, R H A precipitinogen in the serum prior to the onset of acute rheumatism, Jr Exper Med, 1939, lxix, 143-162
- 55 SWIFT, H F The action of sodium salicylate upon the formation of immune bodies, Jr Exper Med, 1922, xxxvi, 735-760
- 56 HANZLIK, P J Actions and uses of salicylates and cinchophen in medicine, Medicine, 1926, vi, 197-373
- 57 COBURN, A F, and MOORE, L V Salicylate prophylaxis in rheumatic fever, Jr Pediat, 1942, xxi, 180-183
- 58 COBURN, A F, and KAPP, E M The effect of salicylates on the precipitation of antigen with antibody, Jr Exper Med, 1943, 173-183
- 59 COBURN, A F Salicylate therapy in rheumatic fever, rational technique, Bull Johns Hopkins Hosp, 1943, lxxiii, 435-464
- 60 LUTWAK-MANN, C The effect of salicylate and cinchophen on enzymes and metabolic processes, Biochem Jr, 1942, xxvi, 706-728
- 61 ABBASSY, M A, HILL, N G, and HARRIS, L J Vitamin C and juvenile rheumatism, with some observations on vitamin C reserves in surgical tuberculosis, Lancet, 1936, ii, 1413-1417
- 62 SWIFT, H F, HITCHCOCK, C H, DERICK, C L, and McEWEN, C Intravenous vaccination with streptococci in rheumatic fever, Am Jr Med Sci, 1931, clxxxi, 1-11
- 63 WILSON, M G, and SWIFT, H F Intravenous vaccination with hemolytic streptococci, its influence on the incidence of recurrence of rheumatic fever in children, Am Jr Dis Child, 1931, xlii, 42-51
- 64 WASSON, V P, and BROWN, E E Immunization against rheumatic fever, Jr Pediat, 1943, xxiii, 24-30
- 65 LAMB, A R Periarteritis nodosa, Arch Int Med, 1914, xiv, 481-516

# CASE REPORTS

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## THE VALUE OF PENICILLIN IN THE CONTROL OF SEPSIS COMPLICATING A CASE OF SEVERE GRANULOCYTO- PENIA (ALEUKEMIC LEUKÈMIA) \*

By VICTOR H KUGEL, Major, M C, A U S, and MAURICE A SCHNITKER,  
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THE VARIETY of agents used to stimulate the bone marrow in neutropenic states has usually produced indifferent (equivocal) results. This has led several investigators to attempt to modify the course of an agranulocytosis by combating the complicating sepsis. According to Dameshek and Wolfson<sup>1</sup> "death (in agranulocytosis) is probably the result of overwhelming sepsis in a body stripped of its granulocyte defenses." These authors reasoned that if sepsis could be controlled until such time as spontaneous recovery of function of the bone marrow might take place, a better therapeutic result might occur. They reported two cases of agranulocytosis occurring after aminopyrine administration which were treated with sulfathiazole (in addition to pentnucleotide, liver extract and transfusions). From the beneficial results obtained, Dameshek and Wolfson felt that the "ensuing recoveries may have been due, in part at least, to the effect of the sulfonamide on the sepsis, thus allowing spontaneous leukocytic regeneration in the bone marrow to take place." Subsequently, Nixon, Eckert and Holmes<sup>2</sup> reported three cases of severe agranulocytosis due to sulfadiazine which recovered following continuation of treatment with large doses of the same drug.

In view of the effectiveness of penicillin against certain infections it seemed reasonable to consider its use under similar circumstances.

Penicillin was employed in the following case with very encouraging results in the control of the mucous membrane lesions and in an apparent prolongation of the patient's life. It has been reported that this new agent can be used without danger in the presence of pronounced anemia, leukopenia or even complete agranulocytosis<sup>3</sup>. Penicillin was used successfully in combating the angina during five attacks of severe neutropenia, in one of which no polymorphonuclear cells were to be found for five days in the peripheral blood. The course of events in this case disclosed the picture of an aleukemic leukemia, with episodes of agranulocytosis, and terminating in frank leukemia believed to be of the monocytic variety. The course of the illness extends over a period of 285 days (nine and one-half months).

### CASE HISTORY

A 28 year old private, of Italian extraction had been under observation in several Army hospitals because of severe headaches. The family history was not contributory. In civil life he had been a pugilist and had had numerous head injuries, including at least "half a dozen knock-outs." His general and neurological examina-

\* Received for publication March 7, 1945

tions on admission were essentially negative except for a bilateral Hoffman sign. The blood and urine were entirely normal. His previous hospital records disclosed several hematologic studies to be well within normal limits.

Approximately one month after admission to the Neuropsychiatric Service of the Valley Forge General Hospital he developed what appeared to be a simple respiratory infection. Within 24 hours he became acutely ill, with a temperature of 103° F, and a pulse of 108. He developed enlarged cervical lymph nodes and a palpable spleen. After transfer to the Medical Service a blood examination showed the hemoglobin to be 90 per cent, red blood cells 4,600,000, white blood cells 5,000 with polymorphonuclear neutrophils comprising 1 per cent, monocytes 53 per cent, and lymphocytes 46 per cent (11 per cent of these were atypical lymphocytes)\*. These findings immediately stimulated an investigation of former medication which disclosed that during the previous month he had received a total of phenobarbital, 0.5 gm, elixir of phenobarbital 120 cc (equivalent of 0.5 gm phenobarbital), aspirin, 0.6 gm, codeine, 0.060 gm, and triple bromides, 2.0 gm. It was thought that none of these were granulocytopenic agents, although barbiturates have been described as a possible cause of agranulocytosis<sup>4</sup>. During the subsequent observation, covering nine and one-half months, no medication other than that detailed was given.

Intensive pentnucleotide therapy was instituted, the patient receiving 2100 cc in seven days despite persistent nausea and paresthesias. In spite of this treatment the illness progressed rather alarmingly, with increasing toxicity, fever, tachycardia, throat inflammation and further enlargement of the cervical lymph nodes and spleen. On the fourth day of the acute illness there appeared severe dysphagia associated with gingivitis and ulceration of the right tonsil. The white blood cell count was now 3,200 with 1 per cent polymorphonuclears, and platelets 102,000 (control 320,000). The tourniquet test was positive. At this point adjuvant penicillin therapy was instituted with the administration of 100,000 units daily in eight divided doses intramuscularly. Within 24 hours there was clinical improvement, although a new ulceration of a tonsil and a harassing productive cough developed. In 48 hours the ulcerations improved and the fever diminished. On this, the tenth day of his acute illness, the peripheral blood contained 3,200 white blood cells with 10 per cent polymorphonuclears. At this time, because of precordial distress, nausea, vomiting, anxiety and generalized numbness, the pentnucleotide was discontinued. The penicillin was continued for nine days, a total of 1,000,000 units being administered. After three more days the polymorphonuclear cells began to increase and by the fourteenth day the blood showed hemoglobin 85 per cent, red blood cells 4,000,000, white blood cells 4,800 with 57 per cent polymorphonuclears, and platelets 254,000 (control 390,000). There was parallel clinical improvement with recession of mouth lesions and lymph nodes and disappearance of the palpable spleen and fever.

For the next week the patient was asymptomatic and afebrile, the white blood cell count remaining level at about 4,000 with 40 to 50 per cent polymorphonuclears. No penicillin was being administered. There then began a decline in all the blood elements until 10 days later (twenty-third day of the illness) the examination showed hemoglobin 75 per cent, red blood cells 3,400,000 and white blood cells 2,100 with 8 per cent polymorphonuclears. During this period of decline, while asymptomatic and with negative physical examination, the patient was given vitamins orally in large doses and liver extract (concentrate) 30 cc daily intramuscularly for eight days. On the thirty-third day of illness hematologic study showed white blood cells 2,100, with 10 per cent polymorphonuclears and the next day, white blood cells 2,500, with 10 per cent polymorphonuclears. During the next eight days the white blood cells ranged between 1,500 and 2,000 with 10 per cent to 40 per cent polymorphonuclears. From

\* Intensive laboratory studies, including hematologic examinations for 115 consecutive days, were carried out. These will not be presented in detail in this report.

the thirty-fourth to the thirty-eighth day the patient received pentnucleotide up to 40 c c daily, to the point of tolerance, without apparent benefit. Yellow bone marrow (Armour) 24 c c or more daily, and ferrous sulfate, 45 grains daily, from the thirty-sixth to the forty-fourth day had no effect on the granulocytes nor on the progressive anemia which also appeared.

On the thirty-seventh day of illness symptoms and signs of sepsis began to reappear. There was mild fever, early gingivitis, mild pain in the neck and jaw and rectal discomfort from perianal inflammation. The next day the temperature was 101° F, there was now also pharyngitis, mild trismus and a recurrence of the cervical lymphadenopathy. On the thirty-ninth day, when the temperature reached 103° F, penicillin, 160,000 Oxford units daily, was begun by intramuscular injection. At this time the gingivae were inflamed and hyperplastic, an erosion had appeared at the angle of the mouth and there was swelling of the left cheek, a necrotic ulceration behind a lower left molar tooth, and a rapidly spreading perianal ulceration. This dosage was continued for 11 days, a total of 1,760,000 units. After 48 hours of penicillin therapy, in the face of a maximum white blood count of 1,800 with 4 per cent polymorphonuclears, there was striking clinical improvement with notable recession of all mouth lesions, a marked decrease of the perianal ulceration, and a temperature not exceeding 100.6° F. The patient then became afebrile and remained so for five days despite the fact that his blood count did not go above 2,000 white blood cells with 22 per cent polymorphonuclears and his red blood cells had dropped to 2,800,000. The anal lesion healed completely, the lip erosion became a clean excavation that required another week for epithelialization. On the fiftieth day he received a transfusion of 250 c c whole blood and the penicillin was discontinued.

A sternal marrow aspiration was carried out on the fifty-fourth day. This revealed a slight decrease in promyelocytes (0.8 per cent), but increased monocytic elements, monocytes 16 per cent and immature monocytes 16.3 per cent. A large number of blast forms were present. Peripheral blood examination at the same time showed hemoglobin 54 per cent, red blood cells 2,800,000, white blood cells 2,500 with polymorphonuclears 5 per cent, lymphocytes 39 per cent, monocytes 6 per cent and immature monocytes 1 per cent. Two consultant hematologists reviewed the sternal marrow specimens and expressed the opinion that the findings were suggestive, but were not conclusive of leukemia.

The third episode of granulocytopenia began on the fifty-eighth day and lasted through the eightieth day of the illness. For a period of 20 days the white blood cell count was never greater than 4,500 with 5 per cent polymorphonuclears, usually 2,500 with 3 per cent neutrophils. For five days no cells of the granulocyte series could be found in numerous smears examined. After 24 hours of significant granulocytopenia penicillin was started again and continued for 21 days. The daily dosage was 100,000 to 160,000 Oxford units intramuscularly, a total of 2,820,000 units being given. During this episode no other treatment was given and the temperature rose but once to 100° in the first 10 days. The patient was given another transfusion of 250 c c whole blood which was followed by a febrile reaction that subsided promptly. Aside from the transfusion reaction and mental depression, the clinical course was surprisingly uneventful. The only detectable changes were a mildly hyperplastic gingivitis, the appearance of a soft apical systolic cardiac murmur, and the development of a palpable liver and spleen extending two fingers' breadth below the costal margin. Toward the end of this relapse the blood picture resembled that of an aplastic anemia with hemoglobin 32 per cent, red blood cells 1,700,000, white blood cells 1,500 with polymorphonuclears 10 per cent, lymphocytes 76 per cent and monocytes 14 per cent.

The general picture of weakness, some cachexia, and the severe depression of all blood elements made the prognosis very doubtful. However, from the eightieth to



the one hundred nineteenth day a striking spontaneous improvement in the blood took place and all elements returned to within normal limits. Two weeks later sternal aspiration was repeated and it was reported that "the values of the various cellular elements of the marrow now approximate the normal range, the previous provisional diagnosis of leukemia cannot be substantiated at this time." Examination of the peripheral blood showed 6,900 white blood cells with 67 per cent polymorphonuclears. The clinical improvement was equally as striking with recovery of strength, weight and well-being.

One month later the patient felt well and physical findings were entirely negative except for a liver and spleen that were barely palpable. The blood picture showed hemoglobin 91 per cent, red blood cells 4,550,000, white blood cells 6,900 with polymorphonuclears 54 per cent, lymphocytes 40 per cent, monocytes 3 per cent and eosinophiles 3 per cent. At this time the patient was transferred to another hospital nearer his home.

*Summary of Subsequent Course* He remained well for one month after transfer. At the end of this period (the remission having lasted 85 days) he relapsed into a fourth episode of severe granulocytopenia with hematologic findings essentially as before. During this period infection was completely controlled with penicillin, 100,000 Oxford units intramuscularly daily for 18 days, totalling 1,800,000 units. In this phase a splenectomy was carried out (neutropenia of splenic origin was considered an indication) but no benefit ensued. The organ weighed 350 gm and microscopically showed pulp hyperplasia with retention of architecture. The pulp contained large numbers of monocyte-like elements focally but it was not thought to be recognizable as a frankly leukemic spleen. Immediately after splenectomy the white cell count rose to nearly normal levels but in eight days granulocytopenia was again present. Penicillin, 100,000 units daily, was given again for 15 days without much change. Forty days after the termination of the fourth relapse, the fifth and last episode of severe granulocytopenia occurred. The patient again received penicillin, 100,000 Oxford units daily, occasionally 200,000 units daily, for 20 days, and no mucous membrane lesions occurred. A leukocytosis then developed that rapidly reached a leukemic level of 246,000. Smears revealed 86 per cent atypical monocytes and monoblasts (equally distributed) and 3 per cent polymorphonuclear cells, a frank picture of monocytic leukemia. He developed complete anorexia, severe vomiting, diffuse pains in the sternum and ribs, abdominal pain, fever, tachycardia and a psychosis. A temperature of 103°-104° F was not affected by penicillin. He died in acute circulatory failure nine days later, nine and one-half months after the onset of his illness.

Necropsy showed the chief leukemic involvement to be in the liver, the epicardium and myocardium, the thymus, bone marrow, and a few lymph nodes. There was no evidence of sepsis in the mouth, lungs, or gastrointestinal tract.

#### COMMENT

This case, as an example of the course of leukemia, though unusual, is not rare. However, the fact that the mucous membrane lesions, presumably occurring from secondary infection when the body is deprived of its normal granulocytic defenses, were controlled very successfully by penicillin therapy prompted us to place it on record. Although several of the sulfonamides have been reported as successfully controlling the ulceration and necrosis of mucous membranes in agranulocytosis, penicillin appeared to us to be a preferable agent for such treatment. Two instances have been reported very recently in which penicillin was used successfully in the treatment of agranulocytosis.<sup>5,6</sup>

Penicillin has a wide range of effectiveness in combating bacterial infection,

and more important, under such circumstances it has been found not to have any noxious effects on the bone marrow or on the elements of the circulating blood. This feature makes it probably much safer to use penicillin to treat infection in a patient with a known bone marrow dyscrasia. The sulfonamides may be equally effective but any one of them has been known to cause bone marrow disturbances in certain individuals. However, in certain instances of sepsis developing during agranulocytosis, when there is a "mixed infection," and some of the invading organisms prove to be insusceptible to penicillin, a combination of penicillin and a sulfonamide may be indicated.

Other drugs, in addition to penicillin, were used in the first and second attacks of granulocytopenia in this patient. The fact that on both occasions the mucosal lesions healed rapidly following the administration of penicillin and that the third, fourth and fifth attacks were treated with penicillin alone, with the prevention of mucosal infection, is noteworthy. This leads one to believe that penicillin is a safe and satisfactory agent in controlling the mucous membrane lesions and other complications of infection that may occur with various stages of leukemia and agranulocytosis. We have no evidence to lead us to believe that the penicillin had any effect on the leukemia per se.

#### SUMMARY

1 This report is concerned with a case of aleukemic leukemia, manifested initially by acute agranulocytosis, with four relapses of severe granulocytopenia and terminating in frank leukemia. All mucous membrane lesions in the five attacks of neutropenia were controlled by the administration of penicillin.

2 In the first attack of neutropenia pentnucleotide was ineffective. Penicillin, however, seemed definitely successful in relieving mucosal ulceration and sepsis. The results of treatment in this attack were considered inconclusive, however, since medications were combined and a spontaneous remission occurred in 14 days.

3 Vitamins and intramuscular liver failed to prevent, nor did pentnucleotide and yellow bone marrow modify, a granulocytopenic relapse of 18 days' duration. Penicillin therapy instituted after the development of ulcerated lesions of the mouth and severe perianal inflammation resulted in a prompt dramatic response despite continuing marked granulocytopenia.

4 A third, most severe, and later fourth and fifth episodes of granulocytopenia were treated from the outset with penicillin alone. No ulcerations or detectable inflammation of mucous membranes occurred. The only significant febrile period developed in the course of a transfusion reaction.

5 Penicillin appears to be effective in combating the bacterial invasion of mucous membranes which frequently occurs when there is marked diminution or absence of circulating granulocytes.

#### BIBLIOGRAPHY

- 1 DAMESHEK, W., and WOLFSON, L. E. A preliminary report on the treatment of agranulocytosis with sulfathiazole, *Am Jr Med Sci*, 1942, cciii, 819.
- 2 NIXON, N., ECKERT, J. F., and HOLMES, K. B. The treatment of agranulocytosis with sulfadiazine, *Am Jr Med Sci*, 1943, ccvi, 713.

- HERRELL, W E, NICHOLAS, D R, and HILMAN, D H Penicillin Its usefulness, limitations, diffusion and detection, with analysis of 150 cases in which it was employed, Jr Am Med Assoc, 1944, cxlv, 1003
- WATKINS, C H The possible rôle of barbiturates and amidopyrine in the causation of leukopenic states, Proc Staff Meet, Mayo Clin, 1933, viii, 713
- SPRAGUE, H B, and FERGUSON, L K Agranulocytosis treated with penicillin, U S Nav Med Bull, 1944, xlii, 1014
- MEREDITH, W C, DOUGLAS, A H R, and FINK, H Penicillin in malignant granulocytopenia, U S Nav Med Bull, 1944, xlii, 1017

## BACK PAIN AS A SYMPTOM OF CARCINOMA OF THE BODY OF THE PANCREAS <sup>1</sup>

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THE diagnosis of carcinoma of the body of the pancreas is rarely made correctly during life or preoperatively. If this condition is considered as a cause of back pain associated with indigestion, especially if aggravated by lying down and relieved by bending forward, in the face of negative physical examination, roentgen-ray and laboratory findings, the diagnosis can be made by exclusion and the patient saved the discomfort of unnecessary investigative procedures and expense. Exploratory laparotomy and biopsy are of course essential for a positive diagnosis. The patient is perhaps helped little by such a diagnosis, but the state of uncertainty is removed and he and his family are spared the trek from doctor to doctor. At present, surgery offers little because the disease is too far advanced by the time significant symptoms develop, though partial resection of the pancreas has been carried out with success by Cattell<sup>1</sup> and Brunschwig<sup>2</sup>. As usual in malignant disease, early diagnosis is essential.

Unfortunately the laboratory offers no good test for pancreatic function. The serum lipase and amylase are increased in only 40 per cent of cases of carcinoma of the pancreas and then only when the disease is far advanced and involves the main duct.<sup>3</sup> The diastase values in the blood and urine are only of value in inflammatory disease of the pancreas and acute pancreatic edema.<sup>4</sup> Anemia is late in its development and there is rarely enough involvement of the islet cells to change the blood sugar. The common bile duct is not involved in the pathologic lesions, so the icteric index is not increased.

The roentgenologist offers some evidence through his negative findings. The gastrointestinal series and barium enema are negative because the duodenal curve is not widened as it is in the more common carcinoma of the head of the pancreas, and displacement as is found in benign cyst of the pancreas is found late, if at all, in carcinoma. The stomach may be involved by direct extension but this evidence comes too late to help the patient. For a complete discussion of the diagnosis of carcinoma of the pancreas, the reader is referred to the articles by Kiefer<sup>5</sup> and Kiefer and Moravec.<sup>6</sup>

In other words it is important to suspect the diagnosis because of the symptom

<sup>1</sup> Received for publication February 19, 1945

complex, namely indigestion and epigastric distress radiating through to the back or accompanied by back pain

In the following case the diagnosis was made preoperatively largely by exclusion after reading the report by Bartels<sup>7</sup>

#### CASE REPORT

A 58 year old white male was first seen on October 20, 1944, because of colicky pains in both lower quadrants of five weeks' duration. There was a story of voluntary weight loss of seven pounds induced by dieting over a period of six months to 175 pounds. In 1928, he was out of work for 11 months because of an obscure abscess in the region of his pituitary gland which he was told had healed without operation. He had always been high strung and nervous and worried considerably about any symptoms though he had continued to work hard even through his present illness.

In July 1944, he had had a complete check up of his vascular system elsewhere and a diagnosis of coronary artery disease and essential hypertension had been made following an electrocardiogram.

Physical examination was entirely negative. Gastrointestinal series revealed some irregularity of the duodenum, at the point where the first portion joins the second portion, which was interpreted as due to scar tissue secondary to some old disease. No active ulcer crater was seen. The barium enema showed spasm of the bowel probably due to an irritable intestinal musculature. Graham test showed no stones and an excellent filling of the gall-bladder. Renal study showed no evidence of stone formation or other renal disease. There were moderately advanced hypertrophic changes in the lumbar spine and sacroiliac joints.

For the next two months indigestion continued in spite of belladonna, pavitrine and phenobarbital, and he began to experience pain in the back below the rib margin. This was particularly troublesome at night or when lying down. It was accompanied by a sense of fullness in the epigastrium which was somewhat relieved by bending forward and by passing urine. His abdominal symptoms became more localized in the epigastrium. He developed anorexia and he continued to lose weight, a total of 15 pounds. He became somewhat more constipated, but developed no melena or change in the character of the stools though they became foul in odor. By the end of January 1945, he developed active vomiting and greater aversion to food. A repeat gastrointestinal series and barium enema showed no change in the previous duodenal deformity, but there was more spasm of the transverse and descending colons.

Physical examination on February 3, 1945, was negative except for tenderness in the epigastrium and the suspicion of a mass below the xiphoid. Rectal examination was negative. A careful neurological examination was negative except for hyperactive reflexes. The red blood count was 4,650,000 with 102 per cent hemoglobin, white blood count 11,800 with a normal differential (2 per cent eosinophiles). The icteric index was 5, the blood sugar 123 mg per cent, and the serum amylase 22 units (normal 20-40 units by the method used). Roentgenogram of the chest showed no evidence of metastases or pulmonary congestion and the heart was within normal limits in size. The stools were positive for occult blood. Reagents for serum lipase were not available.

A tentative diagnosis of carcinoma of the body of the pancreas was made and the patient was explored on February 6, 1945, by Dr Halsey B Loder, who concurred in the diagnosis.

At operation a tumor, the size of an orange, was found in the middle third of the pancreas. This was adherent to the stomach. There were metastases to the

omentum and possibly to the right lobe of the liver. A biopsy was taken which showed metastatic carcinoma which suggests for its origin, the acinar arrangement of the pancreas.

The patient's condition remained good for three weeks after operation. He required from  $\frac{1}{5}$  to  $\frac{1}{4}$  grain of Dilaudid a day for epigastric and back pain. On April 6, he developed clinical jaundice and his liver could be felt two fingers below the costal margin. Cobra venom was tried without any appreciable effect on the pain and it was not possible to reduce the quantity of narcotic during or after its use. He died on April 16, 1945, after four days of semicomatose, seven months after the onset of symptoms.

*Differential Diagnosis* In this patient the following conditions were considered before the diagnosis of carcinoma of the body of the pancreas was made by exclusion.

1 Irritable colon. This condition was found by roentgen-ray, but the lack of clinical response to proper medical management and the increase of pain and its radiation to the back, as time went on, made this diagnosis untenable.

2 Hypertrophic arthritis of the spine with radicular pain. The spine did show hypertrophic changes about the lumbar vertebra, but the location of the pain in the epigastrium as the disease progressed, and the fact that the pain was relieved by bending forward ruled out this possibility.

3 Duodenal ulcer. The scar in the second portion of the duodenum could be interpreted as a penetrating ulcer which could also explain pain radiating through to the back. However, the fact that this scar was unchanged in the subsequent roentgenographic examination and at no time did he develop signs of a localized peritonitis made this diagnosis unlikely.

4 Pancreatic cyst. The severity of the symptoms and the lack of any pressure defect in the outline of the greater curvature of the stomach or of the duodenum by roentgen-ray, plus the severe back pain made this diagnosis unlikely.

## DISCUSSION

The diagnosis of carcinoma of the body of the pancreas should be entertained if

1 There is indigestion with epigastric distress radiating to or accompanied by back pain which is worse on lying down and relieved by bending forward.

2 The serum lipase or amylase is elevated.

3 All laboratory and roentgenographic evidence is normal in the face of persisting epigastric distress.

It is conceivable that surgical cures of carcinoma of the body of the pancreas are possible if early diagnosis can be established.

## SUMMARY

It is possible to make the diagnosis of carcinoma of the body of the pancreas before operation or autopsy if the condition is considered. A case is presented in which the diagnosis was made preoperatively and the condition verified by biopsy.

## BIBLIOGRAPHY

- 1 CATTILL, R. B. Resection of the pancreas, *Surg Clin N Am*, 1943, XLIII, 753-766.
- 2 BRUNSCHWIG, A. The surgical treatment of carcinoma of the body of the pancreas, *Trans 66th Meeting Am Surg Assoc*, May 1944.

- 3 COMFORT, M W, and OSTERBERG, A E Serum amylase and serum lipase in the diagnosis of disease of the pancreas, *Proc. Staff Meet Mayo Clin*, 1940, *xv*, 427
  - 4 PRATT, J A The diagnosis of pancreatic disease, *New York State Jr Med*, 1943, *xliii*, 1847-1855
  - 5 KIEFER, E D Carcinoma of the pancreas, *Arch Int Med*, 1927 *xi*, 1-29
  - 6 KIEFER, E D, and MORAVEC, M The diagnosis of carcinoma of the pancreas, *Surg Clin N Am*, 1943, *xxiii*, 738-746
  - 7 BARTELS, E C Carcinoma of the body of the pancreas, back pain a prominent symptom, *The Lahey Clinic Bull*, 1940, *ii*, 41-46
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### FOLLICULAR LYMPHOMA (BRILL-SYMMERS DISEASE) UN- SUCCESSFULLY TREATED WITH PENICILLIN A CASE REPORT \*

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FOLLICULAR lymphoma (Brill-Symmers disease) is a neoplastic disease of the lymphoid tissues<sup>1</sup>. The average age of onset is 50, the sexes are equally affected, the tumor is localized in approximately 10 per cent of cases, and is responsive to radiation therapy in 95 per cent of cases. It is the least malignant of the malignant lymphoma group, and offers a *relatively* favorable prognosis as judged by the five-year survival rate of 53 per cent. Nevertheless, the 10 year survival rate is but 16 per cent—only twice that of Hodgkin's lymphoma. The eventual fatal outcome of those surviving 10 years and the high rate of transformation into more malignant types of lymphomata,<sup>†</sup> brands non-localized Brill-Symmers disease as a malignant lymphoma with a fatal prognosis. Although the neoplasm is ordinarily widespread, in 10 per cent of the cases it is localized when first observed. Gall,<sup>2</sup> and Gall and Mallory<sup>1</sup> recommend surgical excision as the treatment of choice for all localized malignant lymphomas.

The lethal effect of penicillin upon rat and mouse sarcoma cells has been demonstrated by Cornman.<sup>3</sup> Using induced rat and mouse tumors, he showed that penicillin in "proper dosage" (amount used not stated) killed all the sarcoma cells in roller culture tubes without damaging fibroblasts derived from the same strain of tumor host and grown with the sarcoma cells. (Of the four rat and two mouse tumors one of the mouse tumors showed no such selective response, however.) Large amounts of penicillin also damaged the non-malignant cells, though "the dose required was two or three times that required to produce an equivalent injury in malignant cells."

Biologic confirmation of the killing of the tumor cells was obtained. Penicillin treated tumor cultures were implanted into rats of corresponding 100 per cent susceptible strains in 25 experiments. All the implants from cultures showing lethal damage to tumor cells, and most of those showing "marked damage"

\* Received for publication October 13, 1944

† In 23 per cent there is failure of persistence of histologic type as determined by successive biopsies—i.e., there is dedifferentiation and transition into a lymphoma of more malignant type as the disease progresses. This is evidence for the belief that all the lymphomas are tumors essentially of common origin.<sup>1</sup>

("rounding, coagulation, or disintegration of cells, short of 100 per cent") failed to produce tumors. Implants from "the untreated cultures produced tumors."

In view of Cornman's preliminary report, it was deemed clinically sound to try penicillin therapy in a patient who came under our observation because of widespread involvement of the superficial lymphatic system with follicular lymphoma (Brill-Symmers disease). The use of penicillin for the treatment of our patient also seemed indicated since in this case the condition was widespread with involvement in many portions of the lymphatic system.

#### CASE REPORT

A 25 year old male Air Corps officer first came under our observation April 11, 1944 because of insidious lymph node enlargement involving the inguinal and axillary groups bilaterally. This was first observed by the patient while bathing one year previously (April 1943). The patient states that blood counts and a chest plate at this time were reported as normal. Though he remained asymptomatic, he asked for observation again in March 1944. A biopsy March 15, 1944 of a 2.5 by 1.5 by 0.7 cm lymph node from the "groin" was diagnosed by us and the Army Institute of Pathology as "lymphoid hyperplasia in reactive lymph node."

The family history and the patient's past history were irrelevant. Physical examination revealed an ambulatory, well developed, well nourished male of asthenic habitus. The physical examination was negative throughout except for enlargement of the superficial lymph nodes as follows: There were a few small pea-sized lymph nodes palpable in the posterior cervical chains bilaterally, one almond-sized supraclavicular node palpable on the left, palpable nodes of varying size in the axillae with an isolated node about the size of a small walnut, both visible and palpable, in the left axilla, bilateral questionably enlarged inguinal nodes, and easily visible bilateral femoral nodes, markedly enlarged to palpation. All nodes were discrete, non-tender, and not attached to the adjacent tissues.

The patient's temperature throughout his entire period of observation remained normal. Chest roentgenogram and flat plate of the abdomen were normal and revealed no splenic or lymphatic enlargements.

The admission urine contained a trace of albumin and 10 to 15 white blood cells per high power field, repeated subsequent urinalyses contained neither. Blood Kahn and Wassermann reactions were negative. On admission the blood constituents were as follows: red blood cells 5.2 millions with normal morphology, white blood cells, 6,000, hemoglobin 17.6 grams. Schilling differential count: Eosinophiles 1, non-segmented 2, segmented 66, lymphocytes 29, and monocytes 2. Sedimentation rate was 1 mm in one hour, hematocrit 49 per cent cells, plasma protein 6.2 grams per 100 cc. Complete blood counts repeated at weekly intervals before, during, and following penicillin therapy showed no essential deviation from the initial determinations.

On April 20, 1944, a lymph node was excised from the right femoral region. Histologic examination established the diagnosis of follicular lymphomata (Brill-Symmers disease) which was confirmed by the Army Institute of Pathology (Acc No 109722).

The patient was then given 200,000 units of penicillin per day in doses of 25,000 units intramuscularly at three hour intervals over the 60-day period from April 27 to June 25, 1944, for a total of 11,775,000 units. A second lymph node, left femoral, was excised July 5, 1944. The microscopic characteristics of this lymph node were not distinguishable from those of the right femoral node excised 10 weeks previously, a week before therapy was started. Similarly, the physical findings and clinical course during and following penicillin therapy have remained unchanged to the present (August 1, 1944).



FIG 1 Follicular lymphoma in right femoral lymph node Biopsy, April 20, 1944  $\times 120$



Detailed pathological reports of the two biopsies before and after therapy are as follows

Biopsy April 20, 1944, before penicillin therapy (figure 1)

*Gross* The specimen is a right femoral lymph node measuring 3.5 by 2 by 1 cm, oval and firm, but not of hard consistency. Its surface is covered by a light tan capsule which is smooth and strips easily. The cut surface is uniform yellow-tan.

*Microscopic* (3 blocks, 3 sections, formalin and Zenker's fixed) In one of the sections there are many large ill-defined and loosely filled lymphoid follicles without particular evidence of germinal center hyperplasia. Adjacent lymphoid stroma is relatively scanty in one section. There are no "cracking off" clefts. The lymphoid substance is filled with rather closely packed, uniform and small dark-staining lymphocytes. Despite the hyperchromatism of the nuclei, definite mitoses are rare. There are occasional clasmotocytes and stem cells. There is no fibrosis. Blood vessels are normally abundant and are somewhat thick-walled. Reticulum stained sections show normal amounts or slight excess of the reticulum in the stroma between the follicles, the follicles themselves contain but an occasional strand of reticulum.

The second salient feature is the infiltration of the capsule of the node with uniform, small lymphocytes. These extend into the pericapsular lymphoid tissue. Despite the presence of the capsular infiltration, lymphoid hyperplasia and follicular hypertrophy are so conspicuous as to warrant the diagnosis of follicular lymphoma.

*Diagnosis* Follicular lymphoma (Brill-Symmers disease), right femoral lymph node

Biopsy July 5, 1944, after penicillin therapy (figure 2)

*Gross* The specimen is a left femoral lymph node measuring 4 by 2 by 1 cm. It is covered by a smooth, shiny, firm capsule which is gray in color. On cut section its substance is of a homogeneous yellow-tan appearance.

*Microscopic* This lymph node contains numerous large follicles in which germinal centers are poorly defined or absent. In some fields the follicles blend imperceptibly with the adjacent closely packed lymphoid stroma, and in other fields there is a sharp line of demarcation composed of more closely packed lymphocytes. No definite cleft or "cracking off" is observed. The cells are uniform and there is no proliferation in connective tissue. The lymphocytes extend in some fields irregularly into the adjacent fat so that the capsule of the node is distinguished with difficulty. In other fields the capsule is infiltrated with lymphocytes. Silver stains reveal no increase in reticulum. Eight weeks of penicillin therapy do not appear to have affected this lesion from a histopathologic standpoint.

*Diagnosis* Follicular lymphoma, left femoral lymph node (Brill-Symmers disease)

The diagnosis of follicular lymphoma for each biopsy was confirmed at the Army Institute of Pathology (Acc No 109722), Army Medical Museum, Washington, D. C.

## DISCUSSION

Two aspects of the treatment of this case may well be questioned before the conclusion is drawn that penicillin therapy is without effect in this type of malignancy. The first is the length of time over which the patient was treated and the second is the question of adequate dosage. Concerning the first, we have no specific data upon which to base an opinion. However, since these, as well as all other irradiation sensitive malignancies respond by clinical and histologic regression in much less time than 60 days when treated with effective doses of irradiation, it seemed to us that the patient, if he were going to show improvement, would have done so during the eight weeks of treatment. Also, all other



FIG 2 Follicular lymphoma, left femoral lymph node. Biopsy July 5, 1944, 11 days following completion of 60 days of therapy with penicillin ( $11,775,000 \mu$ )  $\times 120$

conditions in which penicillin is effective show response in less than eight weeks' time

With respect to the question of adequate dosage, the answer is even more difficult. The dosage used by us is known to be effective in all non-malignant, penicillin-sensitive conditions. Coinman<sup>3</sup> found that rat and mouse sarcoma cells were killed by one-third to one-half the penicillin dose required to kill normal cells. The intravenous lethal dose of the sodium salt of penicillin for mice has been determined to be 12,000 units.<sup>4</sup> Assuming comparable toxicity for man, the lethal dose would be 36,000,000 units, and further assuming a comparable ratio of penicillin sensitivity of human sarcoma and normal cells, the lethal sarcoma dose given as a single injection, to man, would be between 6,000,000 and 18,000,000 units. Neither the number of such doses required to destroy human sarcoma (because of the rapid excretion of penicillin from the body) nor the possible toxic effects of such a dose, either single or repeated, are known.

Herrel and Heilman,<sup>5</sup> working with rabbit mesenteric lymph node tissue cultures, determined that in concentrations of less than 42 units per c c, no signs of toxicity were manifest. It has also been determined that rabbit erythrocytes are undamaged by solutions of penicillin containing 42 units per c c,<sup>5</sup> and that human leukocytes are not damaged by concentration of 30 units of penicillin per c c.<sup>6</sup> Again reasoning by analogy from these data and assuming uniform penicillin distribution throughout the tissues, the maximal dosage not producing cytotoxic manifestations in human lymphocytes and erythrocytes in the body would approximate 2,500,000 units. And again utilizing Coinman's ratio of lethal dosage for normal cells compared to sarcoma cells, the lethal dosage for human sarcoma cells, based on rabbit experimentation, would be assumed to be between 800,000 units and 1,250,000 units. Our patient received 25,000 units in single doses at three hour intervals for 60 days for a total dosage of 11,775,000 units. We doubt that he received a sufficient dosage, individual, daily or total, for us to say that penicillin does not have a lethal effect on the lymphoma cells in Brill-Symmers disease. With the dosage used, we can say that there was no demonstrable response in this patient.

### SUMMARY

A case of follicular lymphoma (Brill-Symmers disease) in which penicillin therapy amounting to 11,775,000 units was given over a 60-day period, is reported. Lymph nodes biopsied before and after penicillin therapy revealed no detectable change in the histopathological characteristics of the lesion. Similarly, there was no change in the clinical course and the physical findings following penicillin therapy. It is concluded that penicillin in the amounts given does not alter the course of follicular lymphoma (Brill-Symmers disease).

### BIBLIOGRAPHY

- 1 GALL, EDWARD A, and MALLORY, TRACY B. Malignant lymphoma. A clinico-pathologic survey of 618 cases, *Am Jr Path*, 1942, **LVIII**, 381-429.
- 2 GALL, EDWARD A. The surgical treatment of malignant lymphoma, *Ann Surg*, 1943, **CXVIII**, 1064-1070.
- 3 COINMAN, IVOR. Survival of normal cells in penicillin solutions lethal to malignant cells, *Science*, 1944, **XCIX**, 247.

- 4 ROBINSON, H J Toxicity and efficacy of penicillin, Jr Pharmacol and Exper Therap, 1943, LXXVII, 70-79
- 5 HERRELL, W E, and HEILMAN, D H Tissue culture studies on cytotoxicity of bactericidal agents, Am Jr Med Sci, 1943, CCV, 157-162.
- 6 CHAIN, E, FLOREY, H W, GARDNER, A D, JENNINGS, M A, ORR-EWING, J, SANDERS, A F, and HEATLEY, N G Penicillin as a chemotherapeutic agent, Lancet, 1940, II, 226-228

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## THE USE OF PENICILLIN IN AGRANULOCYTOSIS: CASE REPORT \*

By R W. MOODY, M D and S KAUFAR, M D, F A C P, *Denver, Colorado*

MANY reports of agranulocytosis caused by drug therapy continue to appear in recent medical literature. That aminopyrine can cause this condition has been proved experimentally<sup>1</sup>. Many of the more recent reports are concerned with the rôle of the sulfonamides as causative factors<sup>2</sup>. Some experimental evidence of this has been obtained in animals<sup>3,4</sup>. Because sepsis develops in patients with agranulocytosis and is the main factor which accounts for the high mortality, the sulfonamides have been used in treatment even when they were the suspected etiological agents<sup>5</sup>. The use of penicillin for this purpose would seem more logical as it is usually effective against the types of organism ordinarily responsible for the sepsis. In addition, it has not yet been reported to our knowledge to cause or be associated with any depression of the granulocyte series of the blood.

Agranulocytic angina still carries a high mortality rate and with the increasing acceptance of new drugs which are potential etiological agents, such as thiouracil,<sup>6,7,8</sup> it is important to evaluate penicillin treatment. Furthermore, it is not completely accepted that either transfusion of whole blood, yellow bone marrow concentrate, vitamin concentrates, or pentnucleotide, have any therapeutic effect upon this disease<sup>5,9,10,11</sup>. Because, to date, we have observed only two reports in the literature concerning the use of penicillin in agranulocytosis<sup>12,13</sup> we should like to report the following case.

### CASE REPORT

Mrs E H, a 54 year old woman with chronic bronchial asthma, was receiving pollen extract by injection at intervals throughout the year when on September 12, 1944, following such an injection, she suffered an acute asthmatic attack requiring epinephrine for relief. The following evening she complained of sore throat and sharp, shooting pains in both sides of her neck and head, with swelling of the cervical lymph nodes. The sore throat increased in severity, her temperature rose above normal, and the patient became very toxic. She admitted later having taken the proprietary drug "lumodrin" as a sedative for her asthma. One of us was called to see the woman at her home on September 15, 1944. Examination showed an acutely ill adult white female of the stated age. Temperature was 101° F, and pulse and respirations were increased. A small patch of whitish membrane was present on the throat surrounded by a reddened area. Moderate bilateral anterior cervical lymph-

\* Received for publication March 5, 1945

adenitis was present. Two grams of sulfadiazine were prescribed to be followed by a gram every four hours. Early in the morning of September 17, 1944, the infection had spread throughout the throat and gums and hospitalization was advised. A tentative diagnosis of agranulocytic angina was made.

On admission to the hospital the temperature was 101.2° F, the pulse, 100. There was no further change in symptoms or findings. The rest of the examination aside from the head and neck was essentially negative. The past history revealed not only asthma, but a chronic non-specific ulcerative colitis. She had been hospitalized for this five years previously but had a normal white blood cell count throughout her stay, although sulfonamides were given in the course of treatment. The initial blood count was 1,500 leukocytes of which 2 per cent were polymorphonuclears and 98 per cent lymphocytes. As sulfadiazine was the suspected etiological agent, it was discontinued and pentnucleotide, liver extract, vitamins and bone marrow given. On the second hospital day, the temperature was 103.2° F. Many new inflamed areas covered the throat and gums and Dr. T. E. Carmody, a laryngologist in consultation, agreed it presented the typical appearance of agranulocytic angina. The patient was transfused with 500 cc of whole citrated blood and penicillin was started with a dosage of 20,000 Oxford units intramuscularly every four hours. The patient at this time told of taking the lumodrin, which has the following composition: phenobarbital 0.016 gm, ephedrine 0.024 gm, and aminopyrine 0.130 gm.

| Date    | Highest Temp ° F | Total w b c 1 cu mm | Polymorpho-nuclear Leukocytes | Lympho-cytes | Myelo-cytes | Penicillin in Oxford U |
|---------|------------------|---------------------|-------------------------------|--------------|-------------|------------------------|
| 9/17/44 | 101.2            | 1,500               | 2%                            | 98%          |             |                        |
| 9/18/44 | 103.2            | 1,350               | 0%                            | 100%         |             | 120,000                |
| 9/19/44 | 102.8            | 700                 | 0%                            | 100%         |             | 120,000                |
| 9/20/44 | 103.0            | 800                 | 0%                            | 100%         |             | 120,000                |
| 9/21/44 | 102.0            | 1,050               | 16%                           | 84%          |             | 120,000                |
| 9/22/44 | 98.8             | 2,600               | 56%                           | 44%          |             | 120,000                |
| 9/23/44 | 99.0             | 2,000               | 32%                           | 68%          |             | 120,000                |
| 9/24/44 | 100.6            | 2,950               | 32%                           | 68%          |             | 80,000                 |
| 9/25/44 | 99.8             | 4,900               | 78%                           | 21%          | 1%          |                        |
| 9/26/44 | 98.6             | 6,400               | 68%                           | 32%          |             |                        |
| 9/27/44 | 98.6             | 5,000               | 66%                           | 34%          |             |                        |
| 9/28/44 | 99.2             | 6,800               | 50%                           | 50%          |             |                        |
| 9/29/44 | 98.6             | 8,000               | 66%                           | 34%          |             |                        |
| 9/30/44 | 98.4             | 7,200               | 66%                           | 34%          |             |                        |

A sternal puncture revealed no depression of the myelocyte series. The red blood cell count was 4,000,000, hemoglobin 12.5 gm, platelets 167,000. Heterophile antibody showed no agglutination in any dilution. Streptococcus, Pneumococcus and *Staphylococcus albus* were grown on throat culture. Urinalysis was as follows: yellow, turbid, acid, specific gravity 1.010, trace of albumin, no sugar or acetone, microscopic examination was negative except for a few pus cells.

The patient was transfused twice more and other treatments were continued, but within 72 hours after penicillin was started the fever started to decline, the polymorphonuclear leukocyte count to rise, the lesions in mouth and throat to clear up, and the swollen glands to subside. The patient was less toxic, proceeded to an uneventful recovery, and was discharged from the hospital September 30, 1944. Re-examinations, especially of the blood, at intervals over the past four months have been entirely normal.

In discussion of this case we would like to call attention to the severe sepsis which was the outstanding factor. This was adequately controlled by the penicillin.

cillin until the rise of the polymorphonuclear cell count in the peripheral blood. The sternal marrow examination suggested that this would happen if the patient could be kept alive. The depression in the peripheral blood seemed adequately explained after the patient admitted taking aminopyrine. This was an allergic patient to start with and the acute illness occurred after an asthmatic attack following a pollen injection. Furthermore, the patient was on a strict diet necessitated by a chronic diarrhea of a mild ulcerative colitis and may well have been subclinically deficient in vitamins.

In summary, a case of agranulocytic angina due to aminopyrine is presented in which the use of penicillin seemed to be the primary cause of a spectacular, speedy, and uneventful recovery.

### CONCLUSION

Severe sepsis is the main cause of death in agranulocytosis, and penicillin is effective against the sepsis and is not itself known to depress the granulocytes. It thus has advantages over previous methods of treatment in this condition. When the sepsis is controlled, thereby assisting the patient through a critical period, the removal of the offending agent may then be followed by the regeneration of the granulocytes.

### BIBLIOGRAPHY

- 1 BUTT, E. M., HOFF, A. M., and SOLL, S. N. Experimental production of neutropenia with aminopyrine, *Arch Int Med*, 1939, lxiv, 26-42.
- 2 RINKOFF, S. S., and SPRING, M. Toxic depression of the myeloid element following therapy with the sulfonamides: report of eight cases, *Ann Int Med*, 1941, xv, 89-107.
- 3 AXELROD, A. E., GROSS, P., BOSSE, M. D., and SWINGLE, K. F. Treatment of leukopenia and granulopenia in rats receiving sulfaguanidine in purified diets, *Jr Biol Chem*, 1943, cxlviii, 721.
- 4 DAFT, F. S., and SEBRELL, W. H. The successful treatment of granulocytopenia and leukopenia in rats with crystalline folic acid, *Pub Health Rep*, 1943, lviii, 1542.
- 5 NIXON, N., ECKERT, J. F., and HOLMES, K. B. The treatment of agranulocytosis with sulfadiazine, *Am Jr Med Sci*, 1943, ccvi, 713.
- 6 ASTWOOD, E. B. Treatment of hyperthyroidism with thiourea and thiouracil, *Jr Am Med Assoc*, 1943, cxxii, 78.
- 7 NEWCOMB, P. B., and DEANE, E. W. Thiourea causing granulopenia and thrombopenia, *Lancet*, 1944, i, 179.
- 8 ROSE, E., and McCONNELL, J. Thiouracil in treatment of thyrotoxicosis, clinical experience with 37 cases, *Am Jr Med Sci*, 1944, ccviii, 561-700.
- 9 FORKNER, C. E. Conferences on therapy. The treatment of blood disorders, *Jr Am Med Assoc*, 1940, cxv, 126-131.
- 10 BETHEL, F. H., STURGIS, C. C., MALLORY, O. T., and RUNDLES, R. W. Blood. A review of the recent literature, *Arch Int. Med*, 1944, lxxiv, 131-138.
- 11 JACKSON, H., JR. Leukemia. Agranulocytosis, *New England Jr Med*, 1941, ccxxv, 978-982.
- 12 KEEFER, C. S., ET AL. Penicillin in the treatment of infections. Statement by the committee on chemotherapeutic and other agents, Division of Medical Sciences, National Research Council, *Jr Am Med Assoc*, 1943, cxxii, 1217-1224.
- 13 SMITH, L. B., COHEN, F., and NICHOLS, R. G. Agranulocytosis treated with penicillin, *Jr Am Med Assoc*, 1944, cxxvi, 1027-1028.

## EDITORIAL

### FILARIASIS

Of the exotic tropical diseases with which our military forces have come into contact, filariasis was one of those most unfamiliar to a majority of the physicians of this country. To many of us it chiefly called to mind the grotesque deformities seen in victims of severe infection of long standing, which we had passed by with the feeling that this, at least, was something about which we need have no personal concern. With the employment of troops in the Pacific Islands in which the infection is endemic and almost universal, infections inevitably occurred, and the recognition and management of the disease became an immediate and important problem.

Of the half dozen species of filaria which are known to parasitize human beings, *Wuchereria bancrofti* is by far the most common and wide spread, and it is the only one which has been of any practical importance from the military standpoint. This disease has been a subject of investigation for many years, and the parasite, its life history and mode of spread, and the clinical manifestations of the disease in its fully developed form have been quite familiar to students of tropical medicine. The subject has recently been well summarized by Napier.<sup>1</sup>

The adult parasites are fine, hair-like worms, the females about 5 to 10 cm long and 0.2 to 0.4 mm wide, the males about half this size, which live in the lymphatic vessels and lymph nodes. Man is therefore the definitive host, and may suffer little or no evident injury from the infection. After the worms reach maturity, if conditions are favorable, mating occurs and numerous embryos, microfilariae, are discharged into the lymph and pass through the thoracic duct into the blood. Here they may be taken up by biting mosquitoes, and in a suitable species and under favorable conditions they undergo further development.

In most countries in which the disease is prevalent, *Culex fatigans* is the principal vector, but transmission can be accomplished by a number of other species. It is interesting that the development of this parasite in the *Culex* mosquito and its transmission by the mosquito were described by Manson in 1878, 20 years before the rôle of the mosquito in transmitting malaria was demonstrated. *Culex fatigans* bites chiefly at night. In countries in which this species is the principal vector, the microfilariae are numerous in the blood only during the night, between 10 p.m. and 2 a.m., largely disappearing during the day. There has been much speculation, but no definite proof, as to the mechanism which brings about this periodicity. It is probably connected in some way with the activities of the host, since in individuals who sleep by day and work at night the periodicity is quickly reversed.

<sup>1</sup> NAPIER, L. E. Filariasis due to *Wuchereria bancrofti*, *Medicine*, 1944, XXIII, 149-180

In the Pacific Islands, however, the principal vector is *Aedes variegatus* var *pseudoscutellaris*, a species which bites by day. In these regions the microfilariae do not show any nocturnal periodicity, being most numerous in the blood at about 10 a.m. The phenomenon is evidently an adaptation of the parasite to the biting habits of the vector.

The mosquito is the intermediate host, it is injured more or less severely by the parasites, and if heavily infected dies before development of the parasite is completed.

In the stomach of the mosquito the microfilarial larvae which are about 0.3 mm long and 7.5 micra wide, escape from their sheath and quickly burrow through the stomach wall into the thorax and penetrate between the muscle fibers. They do not multiply in the mosquito, but undergo further growth and development, passing through three larval stages. Under optimum conditions of high external temperature and high humidity, this is completed in from seven to 10 days, but may require two to three weeks. When the third (infective) stage is reached, the larvae which now are 1.5 to 2 mm long and about 20 micra wide, pass forward into the proboscis and enter the labium. When the mosquito feeds, they escape onto the surface of the skin and penetrate either through the puncture wound or probably through the unbroken skin. They are not directly inoculated into the tissues by the bite. The larvae get into the peripheral lymphatics and migrate centripetally into the large lymphatic trunks where they undergo further growth. When mature, mating occurs, and after parturition embryos appear in the peripheral blood. The time required for sexual maturation of the worm after it enters the human host is usually estimated at about a year, but this appears to be quite variable and may be much more than a year.

The symptoms which appear in man depend in part upon the intensity of the infection, on the length of time during which continued reinfection takes place, and perhaps even more upon the reactivity of the tissues of a given individual to the parasite. The clinical manifestations seen in severe cases of the disease represent the accumulated results from repeated reinfection over long periods of time, usually many years, and probably presuppose a high degree of reactivity to the parasite on the part of the tissues of the individuals.

In those cases in which symbiosis is relatively perfect, symptoms may be trivial or negligible and may so continue for long periods. In certain localities in which the bulk of the population is infected, microfilariae have been found in the blood of as high as 54 per cent of those individuals who did not show elephantiasis or other gross manifestations of infection. Frequently, however, the adaptation is less perfect, and the passage of the worms through the lymphatics and lymph nodes excites more or less of an inflammatory reaction. There is considerable evidence that this in large part represents an allergic reaction of the tissues to the foreign protein or secretions of the parasite. If infection is light and infrequent, there may be an



opportunity in the intervals for the inflammatory response to subside. If many parasites are passing through the lymphatics at short intervals, there will be frequently recurring attacks of lymphangitis and lymphadenitis. The normal tissue of the lymph nodes is gradually replaced by eosinophilic granulation tissue and scar tissue, which blocks the lymph channels and eventually leads to obstruction and lymphedema. The recurring attacks of lymphangitis may be accompanied by fever and general systemic symptoms. As time goes on, the tissues of the host probably become more highly sensitized, the inflammatory responses more acute and productive, and the lymphatic obstruction more wide spread and complete. Such phenomena characterize the late stages of the disease.

Concerning the early period of the infection, the many months or years elapsing between the infective bite and the appearance of microfilariae in the blood, little has hitherto been known. It has commonly been regarded as the incubation period or latent symptomless period. Recent observations made in American military forces in heavily infested Pacific Islands, however, indicate that in many cases at least this period is not really symptomless, and that infected individuals present a clinical picture which is fairly typical and easily recognized if searched for.

In the November number of the *Annals of Internal Medicine* are published studies on two series of early cases of filariasis in returning veterans by Leede and Josey<sup>2</sup> and by Goodman et al.<sup>3</sup> In general they confirm observations published by several other writers (Dickson et al.,<sup>4</sup> Haviland,<sup>5</sup> Saphir)<sup>6</sup>. These men had served from two months to two years (on the average a little more than a year) in heavily infested areas during which they had been freely exposed to biting mosquitoes before they made known any complaints. The early symptoms were mild and usually limited to localized pain, tenderness or swelling without notable constitutional manifestations. Common initial symptoms were aching, numbness, weakness of an extremity, which might become quite painful after exertion. This was often associated with palpably enlarged and tender regional lymph nodes. Such symptoms might subside after several hours or a few days, and recur after a number of days or weeks. The femoral, inguinal and axillary nodes were most regularly affected, but often the popliteal and epitrochlears, rarely the cervicals or pectorals. There was sometimes a neighboring lymphangitis with redness and tenderness along the lymphatic trunks. In the intervals pain and tender-

<sup>1</sup> LEEDS, W. E., and JOSEY, A. I. The early diagnosis of filariasis and certain suggestions relative to cause of symptoms, *Ann Int Med*, 1945, xxiii, 816-822.

<sup>2</sup> GOODMAN, A. A., WEINBERGER, E. M., LIPPINCOTT, S. W., MARBLE, A., and WRIGHT, W. H. Studies of filariasis in soldiers evacuated from the South Pacific, *Ann Int Med*, 1945, xxiii, 823-836.

<sup>3</sup> DICKSON, J. G., HUNTINGTON, R. W., and EICHOLD, S. Filariasis in defense force, Samoan group, *U S Nav Med Bull*, 1943, xli, 1240.

<sup>4</sup> HAVILAND, J. W. Recent experiences with filariasis, *Northwest Med*, 1944, xliii, 371-376.

<sup>5</sup> SAPHIR, W. Filariasis. Early clinical manifestations, *Jr Am Med Assoc*, 1945, cxxviii, 1142-1144.

ness subsided, but there remained some degree of lymph node enlargement and sometimes induration and nodular thickening along the vessels

Even more frequent was scrotal involvement, usually unilateral, with nocturnal pain in the testis, pain, tenderness and nodular swelling of the structures of the spermatic cord, less often epididymitis, varicocele or hydrocele appeared. This was commonly associated with a regional lymphadenitis. After subsidence of the acute symptoms, some residual thickening usually remained in the structures of the cord. Rarely there was transient swelling of an extremity.

In a few cases there were recurrent attacks of lymphangitis, either spontaneous or precipitated by exertion. In all cases, however, after removal from the infested areas there was a marked tendency for symptoms and demonstrable pathologic lesions to subside. No elephantiasis or other disabling lesions appeared during the period of observation in Goodman's cases, and were seen in only 0.2 per cent of a larger series.<sup>7</sup>

The diagnosis in these cases was purely clinical, and was based on the known exposure to infection and the similarity (except in severity) of the symptoms and signs to those seen in classical (advanced) cases of the disease. Actual demonstration of the parasite was rarely possible. Attempts to find adult worms in excised lymph nodes were almost always unsuccessful. Microfilariae could rarely be demonstrated in the blood; they were found in only four of 145 cases in the series of Goodman et al. Many attempts have been made to employ for diagnosis complement fixation reactions or intracutaneous tests for hypersensitiveness, utilizing antigens made from *Dirofilaria immitis* from dogs, or some other related parasite. Although positive reactions have been obtained in a substantially higher percentage of these cases than of a control group which had not been exposed to infection, and although these procedures deserve further study, the reactions reported were neither sufficiently sensitive nor specific to be of much value in the diagnosis of individual cases.

When these cases were first encountered, there were no adequate observations available on which an accurate prognosis could be based. Prompt removal of the men from exposure to further infection, symptomatic treatment as required, and general rehabilitation measures during many months' observation have been followed by subsidence of symptoms and largely of local physical signs of the disease in practically all cases. The major problem in the treatment of these men proved to be a psychiatric one. The familiarity of the men with the disease in its advanced stages as seen in the native islanders, the frequent involvement of their own genital organs, the known lack of any specific therapy, and the uncertainty of the medical officers as to the outcome combined to produce a state of keen apprehension which often led to marked psychoneurotic reactions. The effective program of systematic rehabilitation and psychotherapeutic measures which was employed to

<sup>7</sup> ZELIGS, M. A. Psychosomatic aspects of filariasis, Jr. Am. Med. Assoc., 1945, cxcviii, 1139-1142.

combat this has been described by Zelig<sup>7</sup> As the men learned from observations on themselves that the symptoms did subside and that their sexual function was unimpaired, confidence returned except in some fundamentally psychoneurotic individuals

Although it is theoretically possible that the infection might become established in the Southern States where conditions are favorable for propagation of the mosquito (as was once the case in Charleston, S C ), it seems very improbable that this will occur The observations which have been briefly reviewed indicate that the disease will probably not continue to be a problem in this country

## REVIEWS

*American Pharmacy* Edited by RUFUS A. LYMAN, M.D., Dean, College of Pharmacy, Director, Student Health Service, University of Nebraska, Editor, *American Journal of Pharmaceutical Education* J. B. Lippincott Company, Philadelphia 1945 26 × 18.5 cm, 540 pages Price, \$3.00

This comprehensive treatise is a symposium from the pens of more than twenty pharmaceutical specialists. It purports to embrace the fundamental knowledge upon which the practice of pharmacy is based. The three principal divisions of the book are set forth in the title: fundamental principles and practices, pharmaceutical preparations, biologicals.

Part one is preceded by a cogent historical review of pharmacy and its past and present relationship to medicine. The general physical and chemical processes employed in the manufacture of drugs and medicines are given in detail. The physico-chemical principles involved in these procedures are discussed. Among these topics are ionization, colloidal, solubility and extraction of vegetable drugs.

The second part of the volume is concerned with the galenic preparations of the United States Pharmacopoeia and National Formulary. Tinctures, fluidextracts, pills and tablets are among the classes of preparations discussed. The section on ointments and the newer water-soluble ointment bases is worthy of special commendation.

The third section of the book embraces three large classes of biological products used as drugs, namely vitamins, hormones and the sera and vaccines. The responsibility of the pharmacist in handling these products is emphasized and the salient features of their manufacture and therapy are discussed.

In general, the volume fulfills the broad purpose of its editor. The style is good and descriptions are lucid. The reviewer regrets that when therapeutic use is mentioned, the statements are meagre and can scarcely be considered as adequate for pharmaceutical knowledge.

It is hoped that this symposium concept of treatises in pharmacy will be but the forerunner of other volumes in the sciences cognate to pharmacy.

J. C. K., Jr.

## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Experimental Catatonia* By HERMAN HOLLAND DE JONG, M.D. 225 pages, 23.5 × 16 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$4.00

*The Osseous System: A Handbook of Roentgen Diagnosis* By VINCENT W. ARCHER, M.D. 320 pages, 21 × 14.5 cm 1945 Year Book Publishers, Inc., Chicago Price, \$5.50

*The Autonomic Nervous System* Third Edition By ALBERT KUNTZ, Ph.D., M.D. 687 pages, 24 × 16 cm 1945 Lea & Febiger, Philadelphia Price, \$8.50

*A Text-Book of Newo-Anatomy* Fourth Edition By ALBERT KUNTZ, Ph.D., M.D. 478 pages, 24 × 15.5 cm 1945 Lea & Febiger, Philadelphia Price, \$6.50

*Electrotherapy and Light Therapy—with the Essentials of Hydrotherapy and Mechanotherapy* Fifth Edition By RICHARD KOVÁCS, M.D. 694 pages, 24 × 16 cm 1945 Lea & Febiger, Philadelphia Price, \$8.50

- Essentials of Neuro-Psychiatry A Textbook of Nervous and Mental Disorders* By DAVID M. OLKON, S.B., A.M., M.D. 310 pages, 24 × 15.5 cm 1945 Lea & Febiger, Philadelphia Price, \$4.50
- American Pharmacy* Editor in Chief RUFUS A. LYMAN, M.D. Advisory Editors JAMES M. DILLE, Ph.D., ANDREW G. DUMEZ, Ph.D., GLENN L. JENKINS, Ph.D., RUDOLPH A. KUEVER, Ph.G., HUGH C. MULDOON, D.Sc., and HOWARD C. NEWTON, Pharm.D. Technical Editor GEORGE URDANG, Ph.G., D.Sc. Nat. 540 pages, 26 × 18.5 cm 1945 J. B. Lippincott Company, Philadelphia Price, \$8.00
- Physical Chemistry of Cells and Tissues* By RUDOLF HÖBER, University of Pennsylvania School of Medicine, with the collaboration of DAVID I. HITCHCOCK, Yale University School of Medicine, J. B. BATEMAN, Mayo Clinic, DAVID R. GODDARD, University of Rochester, Rochester, N. Y., and WALLACE O. FENN, University of Rochester, Rochester, N. Y. 676 pages, 23.5 × 16 cm 1945 The Blakiston Company, Philadelphia Price, \$9.00
- Manual of Psychological Medicine* Second Edition By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E. 308 pages, 22 × 14.5 cm 1945 The Williams & Wilkins Company, Baltimore Price, \$5.00
- Recent Advances in Obstetrics and Gynaecology* Sixth Edition By ALECK W. BOURNE, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., and LESLIE H. WILLIAMS, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. 357 pages, 20.5 × 14 cm 1945 The Blakiston Company, Philadelphia Price, \$5.00
- Familial Noncaginic Food-Allergy* Second Edition By ARTHUR F. COCA, M.D. 191 pages, 22.5 × 15 cm 1945 Charles C. Thomas, Springfield, Illinois Price, \$3.75
- The Sterilization, Use and Care of Syringes* By a Committee appointed by the Medical Research Council (War Memorandum No. 15) 23 pages, 25 × 15 cm 1945 His Majesty's Stationery Office London Price, \$1.00 (Distributed by British Information Services, 30 Rockefeller Plaza, New York 20, N. Y.)

# COLLEGE NEWS NOTES

## ENLISTMENTS AND RETIREMENTS

### AMERICAN COLLEGE OF PHYSICIANS MEMBERS

Not previously reported among members of The American College of Physicians on active Military Service, is the name of Dr Thomas J Carnicelli, of Frammingham, Mass, who has been on active duty with the Medical Corps, USNR

The total number of members of the College recorded on active duty to date, is 1,928

The following members of the College have been honorably discharged

Maurice James Abrams, Brewton Ala (Lt Col MC, AUS)  
Conrad B Acton, Baltimore, Md (Col, MC, AUS)  
Harry A Alexander, Boulder, Colo (Major, MC, AUS)  
Frank W Anzinger, Springfield, Ohio (Capt, MC, AUS)  
Daniel H Autry, North Little Rock, Ark (Lt Col MC, AUS)  
Walter Hilmar Baer, Manteno, Ill (Capt, MC, AUS)  
M Herbert Barker, Chicago, Ill (Lt Col, MC, AUS)  
Justus M Barnes, Montgomery, Ala (Lt Col, MC, AUS)  
William E G Bayley, La Crosse, Wis (Major, MC, AUS)  
Gerald A Beatty, Wilmington, Del (Major, MC, AUS)  
Carl Burritt Beeman, Grand Rapids, Mich (Major, MC, AUS)  
Orpheus J Bizzozero, Waterbury, Conn (Lt Col, MC, AUS)  
Raymond J Borer, Toledo, Ohio (Lt Col, MC, AUS)  
Edward L Bortz, Philadelphia, Pa (Capt, MC, USNR)  
Albert G Bower, Glendale, Calif (Capt, MC, USNR)  
Bert M Bullington Urbana, Ill (Lt Col, MC, AUS)  
Lewis Thomas Bullock, Los Angeles, Calif (Major, MC, AUS)  
Paul A Burgeson, Warsaw, N Y (Major, MC, AUS)  
J Scott Butterworth, New York, N Y (Capt, MC, AAF)  
Charles Stanford Byron, Brooklyn, N Y (Major MC, AUS)  
James C Cain, Rochester, Minn (Lt Col, MC, AUS)  
Thomas J Carnicelli, Frammingham, Mass (MC, USNR)  
Henry R Carstens, Detroit, Mich (Col, MC, AUS)  
John Richard Cavanagh, Washington, D C (Lt Comdr, MC, USNR)  
Francis H Chafee Providence, R I (Major, MC, AUS)  
William Holmes Chapman, Jr, Suffolk, Va (Major, MC, AUS)  
Milton Henry Clifford, Cambridge, Mass (Lt Col, MC, AUS)  
Sander Cohen, Cincinnati, Ohio (Lt Col, MC, AUS)  
Neil L Crone, Boston, Mass (Col MC, AUS)  
Simon Dack, New York, N Y (Capt, MC, AUS)  
Lucious L Davidge, Shreveport, La (Major, MC, AUS)  
Herman F DeFeo, Chicago, Ill (Lt Col, MC, AUS)  
Douglas Donald, Detroit, Mich (Lt Col, MC, AUS)  
Thomas O Dorrance, Bluffton, Ind (Capt, MC, AUS)  
John M Dyson, Hazelton, Pa (Major, MC, AUS)  
Ralph Arthur Elliott, Gary, Ind (Capt., MC, AUS)  
Earl Bradley Erskine, Evanston, Ill, formerly Jamaica, N Y (Comdr, MC, USN)  
George F Evans, Clarksburg, W Va (Lt Col, MC, AUS)  
I Donald Fagin, New York, N Y (Assistant Surgeon USPHS (R))

Stanley Fahlstrom, Chicago, Ill (Col, MC, AUS)  
 Milton B Filberbaum, Brooklyn, N Y (Lt Comdr, MC, USNR)  
 Eliot E Foltz, Chicago, Ill. (Capt, MC, AUS)  
 Marcel J Foret, New Orleans, La (Major, MC, AUS)  
 Everett C Fox, Dallas, Tex (Comdr, MC, USNR)  
 Israel S Freiman, New York, N Y (Capt, MC, AUS)  
 Meyer Friedenson, New York, N Y (Capt, MC, AUS)  
 Mark W Garry, Milwaukee, Wis (Passed Assistant Surgeon, USPHS (R))  
 Wilton Ross Glenney, Pottsville, Pa. (Major, MC, AUS)  
 John Langdon Gompertz, Piedmont, Calif, now Orinda, Calif (Capt, MC, A  
 Douglas M Gordon, Ponca City, Okla (Major, MC, AUS)  
 William Henry Gordon, Detroit, Mich (Col, MC, AUS)  
 Ghent Graves, Houston, Tex (Capt, MC, USNR)  
 Irving Greenfield, New York, N Y (Capt, MC, AUS)  
 Augustus A Hall, Columbus, Ohio (Lt Col, MC, AUS)  
 William Marion Hall, Shreveport, La (Capt, MC, AUS)  
 James L Hamilton, Chattanooga, Tenn (Major, MC, AUS)  
 Armand William Hanss, Springfield, Mo (Major, MC, AUS)  
 Theodore S Heineken, Jr, Bloomfield, N J (MC, AUS)  
 James Henry Herndon, Dallas, Tex (Capt, MC, AUS)  
 Walter H Hill, San Antonio, Tex (Capt, MC, AUS)  
 Byron Jay Hoffman, Atlanta, Ga (Capt, MC, AUS)  
 Arthur Allan Humphrey, Battle Creek, Mich (Comdr, MC, USNR)  
 Harold L Israel, Philadelphia, Pa (Capt, MC, AUS)  
 Clyde R Jensen, Seattle, Wash (Comdr, MC, USNR)  
 Arvid T Johnson, Rockford, Ill (Capt, MC, AUS)  
 Benjamin Juliar, Detroit, Mich (Capt, MC, AUS)  
 Harry M Kandel, Savannah, Ga (Major, MC, AUS)  
 John Leonard Kantor, New York, N Y (Col, MC, AUS)  
 Paul Sadler Kemp, Macon, Ga (Capt, MC, AUS)  
 Francis E Kenny, Buffalo, N Y (Major, MC, AUS)  
 Milton Kissin, New York, N Y (Major, MC, AUS)  
 Walter O Klingman, New York, N Y (Lt Col, MC, AUS)  
 Leslie R Kober, Phoenix, Ariz (Lt Comdr, MC, USNR)  
 Zeno N Korth, Omaha, Nebr (Lt Col, MC, AUS)  
 Manfred Kjaemer, Newark, N J (Major, MC, AUS)  
 John Edward Leach, Paterson, N J (Lt Col, MC, AUS)  
 Harold D Levine, Boston, Mass (Major, MC, AUS)  
 Howard Avery Lindberg, Chicago, Ill (Lt Col, MC, AUS)  
 Charles H Lutterloh, Hot Springs National Park, Ark (Col, MC, AUS)  
 Thomas B Magath, Rochester, Minn (Capt, MC, USNR)  
 Julian E McFarland, Ames, Iowa (Comdr, MC, USNR)  
 Frank B McGlone, Denver, Colo (Major, MC, AUS)  
 Charles A McKendree, New York, N Y (Capt, MC, USNR)  
 John Fleck Miller, Newark, Ohio (Major, MC, AUS)  
 Tate Miller, Dallas, Tex (Lt Comdr, MC, USNR)  
 Samuel Mirsky, Ottawa, Ont, Can (Major, RCAMC)  
 Morris E Missal, Rochester, N. Y (Lt Col, MC, AUS)  
 Robert S Palmer, Boston, Mass (Capt, MC, USNR)  
 Orman C Perkins, Brooklyn, N. Y (Comdr, MC, USNR)  
 Horace Pettit, Philadelphia, Pa (Major, MC, AUS)  
 John M Porter, Concordia, Kan (Comdr, MC, USNR)  
 Harold Walter Potter, New Brunswick, N. J (Lt Col, MC, AUS)

John F Rainey, Anderson, S C (Capt, MC, AUS)  
 Harold L Rakov, Kingston, N Y (Comdr, MC, USNR)  
 John Patrick Rattigan, Brighton, Mass (Lt, MC, USNR)  
 Jack Rom, Detroit, Mich (Capt, MC, AUS)  
 Edward Still Ross, Dallas, Tex (Lt Comdr, MC, USNR)  
 E Driver Rowland, Hot Springs, Ark (Major, MC, AUS)  
 Milton Jerome Rueger, Detroit, Mich (Capt, MC, AUS)  
 J Griswold Ruth, Flint, Mich (Capt, MC, AUS)  
 William Saphir, Chicago, Ill (Major, MC, AUS)  
 Sidney Schnur, Houston, Tex (Capt, MC, AUS)  
 John Bernard Schwedel, New York, N Y (Lt Comdr, MC, USNR)  
 Stanley D Simon, Cincinnati, Ohio (Major, MC, AUS)  
 Howard Nellson Simpson, Woburn, Mass (Major, MC, AUS)  
 Kenneth McLane Smith, Columbus, Ohio (Lt Col, MC, AUS)  
 William Lester Smith, Carbondale, Ill (Senior Surgeon, USPHS)  
 Maurice Sokolow, San Francisco, Calif (Lt, MC, USNR)  
 Mitchell A Spellberg, Chicago, Ill (Major, MC, AUS)  
 Brandt Ferguson Steele, Indianapolis, Ind (Major, MC, AUS)  
 Edwin Chester Swift, Jacksonville, Fla (Comdr, MC, USNR)  
 Boen Swinny, San Antonio, Tex (Lt Col, MC, AUS)  
 Robert T Terry, Denver, Colo (Major, MC, AUS)  
 Henry M Thomas, Jr, Baltimore, Md (Col, MC, AUS)  
 George C Turnbull, Evanston, Ill (Lt Col, MC, AUS)  
 Eugene L Walsh, Evanston, Ill (Major, MC, AUS)  
 George Wilks Warrick, Birmingham, Ala (Lt Col, MC, AUS)  
 Willard H Willis, Utica, N Y (Major, MC, AUS)  
 Walter J Wilson, Jr, Detroit, Mich (Capt, MC, AUS)  
 Donald J Wolfram, Indianapolis, Ind (Lt Col, MC, AUS)  
 Stuart Yntema, Saginaw, Mich (Lt Col, MC, AUS)  
 John I Zarit, Denver, Colo (Major, MC, AUS)

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#### NEW LIFE MEMBERS

The following Fellows of the College have become Life Members

Dr Ernest Dexter Hitchcock, Great Falls, Mont  
 Dr Johannes Maagaard Nielsen, Los Angeles, Calif

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#### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged

##### *Books*

Malcolm T McEachern, F A C P, Associate Director, American College of Surgeons, Chicago, Illinois—Volumes I and II, "The Joy of Living," autobiography by the late Dr Franklin H Martin, "Digest of the Proceedings of the Council of National Defense during the World War," by the same author



*Reprints*

Nathan Blumberg, F A C P, Philadelphia, Pa —1 reprint  
 Richard D Kepner, F A C P, Honolulu, T H —2 reprints  
 John E Leach, F A C P, Lieutenant Colonel, (MC), AUS—1 reprint  
 Laurence H Mayers, F A C P, Chicago, Ill —2 reprints  
 Frederick Mulsow, F A C P, Cedar Rapids, Iowa—1 reprint  
 Joseph F Painton, F A C P, Lieutenant Colonel, (MC), AUS—1 reprint  
 William Stein, (Associate), New Brunswick, N J —3 reprints  
 Burton L Zohman, F A C P, Brooklyn, N Y —2 reprints

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The Oklahoma City Annual Fall Clinics were held November 24-25 Dr Ernest E Irons, F A C P, President of the College, was a guest speaker

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## THE AMERICAN COLLEGE OF PHYSICIANS REGIONAL MEETING HELD IN CHICAGO

The Annual Regional Meeting for Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin was held at the Hotel Continental, Chicago, November 10, 1945, under the chairmanship of Dr LeRoy H Sloan, F A C P, Regent The Executive Committee consisted of the Governors of the College for the participating States

The meeting was featured as the concluding session of The American College of Physicians Postgraduate Course in Endocrinology, under Dr Willard O Thompson, F A C P, November 5-10, and as the introductory session to The American College of Physicians Postgraduate Course in Gastro-enterology, directed by Dr Walter L Palmer, F A C P, at the University of Chicago, November 12-17 Furthermore, this Regional Meeting was a joint session with the War-Time Graduate Medical Meetings, and a Medical Conference of the Sixth Service Command and Adjoining Areas The attendance was approximately 400 The scientific program was as follows

*Morning Session*

## 1 Clinico-Pathological Conference

EDWIN F HIRSCH, M D, Ph D (by invitation), Director, Department of Pathology, St Luke's Hospital, and JOSIAH J MOORE, M D, Ph D, F A C P, Director, Moore Clinical Laboratory, Chicago

## 2 Ruptured Intracranial Aneurysms

ADOLPH L SAHS, M D (Associate), Acting Head, Department of Neurology, and Associate Professor, State University of Iowa College of Medicine, Iowa City

## 3 Present Status of Penicillin in the Treatment of Syphilis

ROBERT M CRAIG, M D (Associate), Past Assistant Surgeon, U S Public Health Service, Co-Director, Chicago Intensive Treatment Center

## 4 The Clinical Significance of the Rh Factor

ELMER L DELGOWIN, M D (by invitation), Associate Professor in the Department of Internal Medicine State University of Iowa College of Medicine, Iowa City

## 5 The Role of Amino Acids in Protein Metabolism (Experimental Studies)

PAUL M CANNON, M D, Ph D (by invitation), Professor of Pathology and Head of the Department, University of Chicago

## 6 Endocrine Causes of Sterility

E C HAMBLAN, M D, F A C S (by invitation), Associate Professor of Gynecology and Obstetrics, Duke University School of Medicine, Chief of Endocrine Division and Endocrinologist, Duke Hospital, Durham, N C

## 7 Endocrine Regulation of Menstruation

JOSEPH E MARKEE, Ph D (by invitation), Professor of Anatomy, Duke University School of Medicine Durham, N C

## 8 Antihormones

KENNETH W THOMPSON, M D (by invitation), Managing Editor, Journal of Clinical Endocrinology, Clinical Professor of Surgery, Tufts College Medical School, Boston

## 9 The Use of Concentrated Human Albumin in the Treatment of Edema of Renal and Hepatic Origin

GEORGE W THORN, M D, F A C P, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, Physician-in-Chief, Peter Bent Brigham Hospital, Boston

*Luncheon Address*

## The Nutrition Picture in Italy

ELMER L SEVRINGHAUS, M D, F A C P, Professor of Medicine, University of Wisconsin Medical School, Madison

*Afternoon Session*

## MILITARY MEDICINE AND CIVILIAN PRACTICE

## The Application of the Experiences Gained in Military Medicine to Daily Practice in Civilian Life

## 1 Infectious Hepatitis

M HERBERT BARKER, M D, F A C P, Chicago, Assistant Professor of Medicine, Northwestern University Medical School, formerly Colonel, Medical Corps, Consultant in Hepatitis, Allied Force Headquarters, Mediterranean Theater

## 2 Acute Respiratory Diseases

WESLEY W SPINK, M D, F A C P, Associate Professor of Medicine, University of Minnesota, Minneapolis

## 3 Tropical Infections

COL HENRY M THOMAS, M D, F A C P, Consultant in Medicine, Southwest Pacific Area, former Governor and Vice President of American College of Physicians, Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore

## Discussion by

LT COL MYLES P BAKER, M D (by invitation), Medical Consultant, Headquarters, Sixth Service Command

J ROSCOE MILLER, M D, F A C P, Dean, Northwestern University Medical School Chicago

## 4 Neuropsychiatry

ROY R GRINKER, M D (by invitation), Director of the Psychosomatic and Psychiatric Institute of Michael Reese Hospital, Chicago

## 5 Peripheral Vascular Diseases

## (a) Medical Aspects

MAJOR DAVID ABRAMSON M D, F A C P, Mayo General Hospital, Galesburg, Ill

## (b) Surgical Aspects

LT COL HARRIS B SCHUMACKER, M D (by invitation), Mayo General Hospital, Galesburg, Ill

## 6 Educational Facilities for the Returning Medical Officers

VICTOR JOHNSON, M D, Ph D (by invitation), Secretary, Council on Medical Education and Hospitals, American Medical Association, Chicago

## 7 Planning for Future Hospital Needs

OTIS L. ANDERSON, M D, F A C P, Hospital Division, U S Public Health Service, Washington, D C

At a meeting of the Board of Regents at Philadelphia, November 18, 1945, the following elections to membership in the College were made

*Elections to Associateship*

- |   |  |
|---|--|
| Akin, John Marvin, Birmingham, Ala        | Elliott, Robert William, St Louis, Mo,     |
| Alberhasky, Robert James, Louisville, Ky. | (MC), AUS                                  |
| Alderman, Jerome Elliot, Syracuse, N Y.   | Elstei, Benjamin Burt, Port Arthur, Tex    |
| Alpert, Barnett, Brooklyn, N Y            | Fischer, Jacob Warren, Chicago, Ill        |
| Asher, Leonard Max, Los Angeles, Calif,   | Fisher, A Murray, Baltimore, Md            |
| (MC), AUS                                 | Flatow, Jerome Harold, Syracuse, N Y.      |
| Auerbach, Oscar, Staten Island, N. Y.,    | Goldfarb, Walter, New York, N Y.,          |
| (MC), USNR                                | (MC), AUS                                  |
| Avery, Noyes Latham, Jr, Ann Arbor,       | Guss, John Hiner, Staunton, Va             |
| Mich, (MC), AUS                           |  |
| Baldwin, Arthur Dwight, Wellesley,        | Hargis, William Huard, Jr, San Antonio,    |
| Mass, (MC), AUS                           | Tex, (MC), AUS                             |
| Barnes, Malcolm Lynn, Louisville, Ky.,    | Harvey, Robert Philip, Denver, Colo,       |
| (MC), AUS                                 | (MC), AUS                                  |
| Barnett, William Edwin, Logansport,       | Herbut, Peter Andrew, Philadelphia, Pa     |
| Ind, (MC), AUS                            | Hobbs, Thomas Gideon, Chicago, Ill,        |
| Briggs, Ward Wright, Wilmington, Del,     | (MC), AUS                                  |
| (MC), USNR                                | Hodell, George Richard, Houston, Tex       |
| Brill, Norman Quintus, New York, N. Y.,   | Hodil, Elmer Raleigh, Allenwood, Pa        |
| (MC), AUS                                 | Horan, Michael Joseph, Jr, Rochester,      |
| Brugsch, Heinrich Georg, Boston, Mass,    | Minn                                       |
| (MC), AUS                                 | Hubbard, Milton Edward, Los Angeles,       |
|   | Calif, (MC), AUS                           |
| Cayer, David, Winston-Salem, N C          | Hynes, Kyran Robert Emmett, Seattle,       |
| Chapman, Don Wilton, Houston, Tex         | Wash                                       |
| Clark, Thomas Edison, Columbus, Ohio,     |  |
| (MC), USNR                                | Indelicato, Joseph Carlino, Brooklyn,      |
| Clemmer, John Jasper, Albany, N Y.        | N. Y                                       |
| Close, Henry Pletcher, Philadelphia, Pa   |  |
| Cohen, Samuel E, Binghamton, N Y          | January, Lewis Edward, Iowa City,          |
| Coventry, William Dean, Duluth, Minn.,    | Iowa, (MC), AUS                            |
| (MC), AUS                                 | Jeffers, William Allen, Philadelphia, Pa., |
|   | (MC), AUS                                  |
| Darrow, Arthur Charles, St Louis, Mo,     | Jones, Granville Lillard, Marlboro, N. J.  |
| (MC), AUS                                 |  |
| Derbes, Vincent Joseph, New Orleans,      | Kaliski, Sidney Richard, San Antonio,      |
| La  | Tex  |
| Dewey, George, Washington, D C            | Kasich, Milosh, Weehawken, N. J.,          |
| Dickie, Helen Aird, Madison, Wis          | (MC), AUS                                  |
| Di Gregorio, Nicholas John, Brooklyn,     | Kimball, James LeRoy, Salt Lake City,      |
| N Y., (MC), AUS                           | Utah                                       |
|   | Kimbro, Robert Willis, Cleburne, Tex,      |
| Ecler, Henry Dunlop, Washington, D        | (MC), AUS                                  |
| C, USPHS                                  |  |

Klatskin, Gerald, New Haven, Conn,  
(MC), AUS

Levi, J Elliot, Baltimore, Md, (MC),  
AUS

Levinson, Julian Paul, Pittsburgh, Pa

Levy, Herman Abraham, Chicago, Ill

Libin, Isaiah Edward, New York, N. Y.,  
(MC), AUS

Linsman, Joseph Francis, Washington,  
D C, (MC), USA

Lustok, Mischa J, Milwaukee, Wis,  
(MC), AUS

Lyons, Harold Aloysius, Washington,  
D C, (MC), USN

Mares, Lumir Martin, Wenatchee, Wash,  
(MC), AUS

Marquis, Harold Henry San Francisco,  
Calif, (MC), AUS

McTavish, Willson Alexander, Toronto,  
Ont, Can

Mendell, Theodore H, Philadelphia, Pa,  
(MC), AUS

Merves, Louis, Philadelphia, Pa, (MC),  
AUS

'Morris, Milton Howard, Far Rockaway,  
N Y

Nay, Richard Marion, Rochester, Minn,  
(MC), AUS

Nolan, Don Edwin, Dayton, Ohio, (MC),  
AUS

Odle, Sidney G, Pittsburgh, Pa

Pierce, Leslie Staebler, Greensburg, Pa,  
(MC), AUS

Pohl, Arnold Waite, Albany, N Y

Powell, William Nottingham, Temple,  
Tex

Pullen, Roscoe LeRoy, New Orleans, La

Robinson, Joseph Franklin, 'Wilkes-  
Barre, Pa

Rosove, Leon, Santa Monica, Calif,  
(MC), USNR

Rotter, Saul David, West Palm Beach,  
Fla

Rupp, John Jerome, Santa Barbara,  
Calif, (MC), USNR

Rutherford, Robert Bruce, Peoria, Ill,  
(MC), AUS

Sauvageot, John Paul, Akron, Ohio,  
(MC), AUS

Savage, Charles Linwood, Penns Grove,  
N J

Shields, Ralph Kenneth, Bethlehem, Pa,  
(MC), AUS

Shulack, Norman Richard, Brooklyn, N  
Y, (MC), AUS

Smith, Leshe Benjamin, Phoenix, Ariz,  
(MC), AUS

Spicknall, Charles Gassaway, Washing-  
ton, D C, USPHS

Stem, Irwin Daniel, Mt Vernon, N Y,  
(MC), AUS

Talkov, Robert Harold, Boston, Mass,  
(MC), AUS

Tarr, Leonard, New York, N Y, (MC),  
AUS

Texon, Meyer, New York, N Y

Townsend, Leslie M, Roselle Park, N J

Veatch, Everett Parker, Pasadena, Tex

Vickers Martyn Andrew, Bangor, Maine

Vilter, Richard William, Cincinnati, Ohio

Wachstein, Maximilian, Middletown,  
N Y

Waldman, Samuel, Brooklyn, N Y

Webb, Richard Fouke, Pasadena, Calif,  
(MC), AUS

Weickhardt, George Davis, Washington,  
D C

White, Paul Luke, Austin, Tex, (MC),  
AUS

Wood, Donald Eugene, Indianapolis,  
Ind, (MC), AUS

Wright, Donovan George, Washington,  
D C, (MC), USN

Zeis, Leander Bernard, Houston, Tex

Zeman, Frederic David, New York, N Y

*Elections to Fellowship*

- Agnew, George Harvey, Toronto, Ont, Can
- Andrews, Cecil Lenzora, Washington, D C, (MC), USN
- Arndt, Karl Frederick, Denver, Colo, (MC), AUS
- Arnold, Harry Loren, Jr, Honolulu, T H
- Baer, Samuel, Philadelphia, Pa
- Bauerlein, Theodore Charles, Salt Lake City, Utah
- Berliner, Kurt Joseph, New York, N Y
- Bradford, Henry Alexander, Detroit, Mich, (MC), AUS
- Briggs, John Francis, St Paul, Minn
- Clagett, A(ugustus) Henry, Jr, Philadelphia, Pa
- Clement, David Hale, Buffalo, N Y, (MC), AUS
- Cohen, Abraham George, New York, N Y, (MC), AUS
- Cohen, Samuel James, Brooklyn, N Y
- Comeau, Wilfrid Joseph, Bangor, Maine, (MC), AUS
- Dack, Simon, New York, N Y
- Dawber, Thomas Royle, Washington, D C, USPHS
- Dine, William Clay, Jr, Amarillo, Tex, (MC), AUS
- Donovan, Maurice Anthony, Schenectady, N Y
- Engelhardt, Hugo Tristram, Houston, Tex
- Eppinget, Eugene Charles, Boston, Mass, (MC), AUS
- Fcamilla, Roberto Francisco, San Francisco, Calif, (MC), AUS
- Evans Edgar Ernest Penns Grove, N J
- Fagin, I(rving) Donald, Detroit, Mich, USPHS (R)
- Feder, Isidore Albert, Brooklyn, N Y, (MC), AUS
- Fen Harry David, New York, N Y, (MC), AUS
- Fisher, James Brookbank Wichita, Kan
- Flynn, John Molloy Boston, Mass
- Foran, Francis Leo Chicago, Ill
- Foulgei, Margaret P H, Philadelphia, Pa
- Green, Harold David, Winston-Salem, N C
- Hathhorn, Harold Ellsworth, Youngstown, Ohio, (MC), AUS
- Hopkins, B Smith, Jr, Urbana, Ill
- Houston, Robert Alexander, Sunbury, Pa
- Jaffe, Louis, Detroit, Mich, (MC), AUS
- Jones Stewart Hayner, Boston, Mass
- Joyce, Frank Thomas, Chickasha, Okla., (MC), AUS
- King, Boyd G, Cleveland Heights, Ohio, (MC), AUS
- King, William David, Washington, D C, USPHS
- Kinsey, Roy Elias, Peekskill, N Y, (MC), AUS
- Kotte, John Harold, Cincinnati, Ohio
- Kruger, Alfred Leon, Jersey City, N J., (MC), AUS
- Kurz, Edward Royal Henry, Brooklyn, N Y, (MC), AUS
- Kyser, Franklin Arthur, Evanston, Ill
- LeWinn, Edward Bernard, Philadelphia, Pa
- Lewis, Leon, New York, N Y, (MC), USNR
- Lilga, Harris Vincent Petoskey, Mich, (MC), AUS
- Lipschutz, Louis Sanderson, Detroit, Mich, (MC), AUS
- Lynch, John Phillip, Richmond Va
- Manchester, Robert Case, Norfolk, Va, (MC) USNR
- Marshall, Edward Allen, Cleveland, Ohio, (MC), AUS
- Massie, Edward, St Louis, Mo
- McCloskey, Bernard J, Johnstown, Pa
- McFarland, Julian Ewart, Ames, Iowa, (MC), USNR
- Melamed, Samuel, New York, N Y, (MC), AUS
- Meneely, George Rodney, Nashville, Tenn

|  |  |
|--|--|
| Michalover, Saul, Brooklyn, N Y,<br>(MC), AUS                | Soffer, Louis Julius, New York, N<br>Solomon, Saul, New York, N Y, (M<br>AUS |
| Newburger, Robert Anton, New York,<br>N Y, (MC), AUS         | Steinberg, Morris Feldman, Brool<br>N Y, (MC), AUS                           |
| Parks, Harry, Atlanta, Ga                                    | Stuart, Charles Keith, Hamilton, (   |
| Peake, John Day, Mobile, Ala                                 | Can  |
| Raab, Wilhelm Burlington, Vt                                 | Taub, Samuel James, Chicago, Ill   |
| Reeser, Richard, Jr, Daytona Beach, Fla                      | Tempel, Carl Willard, Washington<br>C, (MC), USA                             |
| Reinhart, Harry Louis, Columbus, Ohio                        | Thomas, Paul Jasper, Dallas, Tex   |
| Rippy, Edwin Luther, Dallas, Tex,<br>(MC), AUS               | Van Alstyne, Walter Kent, Bingham<br>N Y                                     |
| Russek, Henry Irving, Brooklyn, N Y,<br>USPHS (R)            | Withers, Orval Raymond, Kansas (   |
| Saxe, Earl Topeka, Kan, (MC). AUS                            | Mo   |
| Schiller, Israel Abraham, Brooklyn, N<br>Y, (MC), AUS        | Yeager, Robert Lee, Jr, Pomona, N  |
| Schwartz, Louis Adrian, Detroit, Mich,<br>(MC), USNR         | Young, Ellis William, Pittsburgh,<br>(MC), AUS                               |
| Shutkin, Michael W, Milwaukee Wis                            | Ziskin, Thomas, Minneapolis, M   |
| Smith, Kenneth McLane, Columbus<br>Ohio, and Pasadena, Calif | (MC) AUS   |

The Committee on Fellowships and Awards met at the College Headquarter November 17 and carefully considered the credentials of five applicants for Research Fellowships in Medicine for a period of one year beginning January 1, 1946, with annual stipend ranging from \$1,800 to \$2,500

At its meeting held on November 18, the Board of Regents awarded a Research Fellowship in Medicine to Dr Kenneth Austin Evelyn of Montreal, Canada, to work in the Department of Pathology, McGill University, under Professor Duff, and at Royal Victoria Hospital under Dr Jonathan Meakins, on the Pathogenesis and Treatment of Hypertension. Dr Evelyn has already made his mark in scientific clinical research and served with distinction as Commander of the Biophysics Laboratory of the RCAF in Montreal.

The Committee also carefully studied nine other applications for Clinical Fellowships in Medicine for the year 1946, with an annual stipend ranging from \$1,800 to \$3,000, depending on individual circumstances. These Clinical Fellowships start at any time during 1946 and are not renewable. They are designed primarily for physicians honorably discharged from the Armed Forces who are Fellows, Associates or prospective candidates for Associateship in the College. The Committee recommended Clinical Fellowships for five of the nine candidates.

Dr Joseph Michael Barker, Arlington, Virginia  
to work with Dr Frank Wilson at the University  
of Michigan Hospital

Dr Norman Leo Cressy, Beverly, Massachusetts  
to work in the Department of Medicine Yale  
University under Dr Francis G Blake

Dr John Bamber Hickam, Dayton, Ohio,  
to work with Dr Eugene Stead at Emory  
University, Atlanta, Georgia

Dr John Scott Hunt, Lexington, Kentucky,  
to work with Dr Hugh Morgan at Vanderbilt  
University, Nashville, Tennessee

Dr Philip Anthony Tumulty, Washington, D C,  
to work with Dr Warfield Longcope at the  
Johns Hopkins Hospital, Baltimore, Maryland

The Committee invites attention to the fact that funds are still available for two additional Research Fellowships for 1946, and that applications may be submitted not later than April 1, 1946. Four or five additional Clinical Fellowships may be awarded to outstanding candidates at any time during the coming year, preferably before April 1, 1946. Further information and application blanks may be obtained by contacting the Educational Director at 4200 Pine Street, Philadelphia 4, Pa

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The Committee on Educational Policy of the Board of Regents, at a meeting at the College Headquarters on November 17, approved in general the following outline of proposed postgraduate courses for the Spring and Autumn of 1946 (Number of courses indicated in parenthesis)

Allergy (2), Arthritis (3), Cardiology (2), Chemo-therapeutics (1), Chest Diseases (2), Gastro-enterology (3), General Medicine (3), Hematology (1), Internal Medicine (4), Metabolic Diseases and Nutrition (1), Pathological-physiology of Disease (1), Peripheral Vascular Diseases (2), Psychiatry and Neurology (2), Psychosomatic Medicine (1)

The details of organization of these courses will be worked out by the Office of the Educational Director and, when available, a prospectus will be sent to each Member of the College, listing the location, duration and Director of each course. Watch for further announcements in succeeding issues of this journal

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The Educational Director has been in touch with each Regent and Governor of the College, requesting information concerning available residencies in medicine, assistantships, teaching positions and research assignments throughout the country in an attempt to organize a helpful postwar program for the benefit of our returning medical officers from the Armed Forces. At the present writing some 1,600 members of the College are still in uniform, serving their country. The majority of these medical officers will be returned to an inactive duty status within the next three to six months, or sooner. One of the functions of the Educational Director is to provide, in so far as possible, personal counsel and advice in the matter of further training for our younger veteran members, and a list of desirable locations for the practice of Internal Medicine and its allied specialties for older medical officers upon their release from active military duty.

The College in no way will act as a placement bureau but will endeavor to secure information of value in allocating and aiding transition of Reserve Medical Officers in their return to civilian medicine.

The College requests all Members in civilian life to forward immediately to its Educational Director any information concerning available residencies, assistantships, teaching positions and research assignments and/or desirable places for the practice of Internal Medicine.

The meeting was concluded in the evening with a dinner session and an address by Dr Robert S Stone, Professor of Radiology, University of California, and Visiting Professor of Roentgenology, University of Chicago, on "The Implications of the Atomic Age for Medicine"

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Colonel Henry M Thomas, Jr, F A C P, Consultant in Medicine, 1943-1945 Southwest Pacific Area, and AFWESPAC, addressed the Medical Conference of the Sixth Service Command at the Drake Hotel, Chicago, Ill, November 9, on "Schistosomiasis Japonica"

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The American College of Radiology has announced the first of a projected series of postgraduate courses sponsored by that organization in conjunction with selected teaching institutions, during the week of February 4, 1946, at the Philadelphia County Medical Society Building. This first and experimental course, patterned after similar courses conducted by The American College of Physicians and The American College of Surgeons, will be jointly sponsored by The American College of Radiology and The Philadelphia Roentgen Ray Society. The course will be under the direction of Dr Eugene Pendergrass, F A C P, of the University of Pennsylvania. The course will include practical consideration of therapy problems concerned with the physics of radium and roentgen rays, carcinoma of the female genital tract, carcinoma of the breast, carcinoma of the head and neck, carcinoma of the skin, treatment of infections, radiation treatment of blood dyscrasias and lymphoblastomas, cancer detection clinics and important developments in cancer research.

Advance registrations should be made with the Commission on Education, American College of Radiology, 20 N Wacker Drive, Chicago 6, Ill

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The 15th Annual Spring Clinical Conference of the Dallas Southern Clinical Society will be held at the Hotel Adolphus Dallas, Tex, March 18-21 inclusive, 1946

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#### LIEUTENANT COMMANDER M LEONARD GOTTLIEB LIBERATED

Lieutenant Commander M Leonard Gottlieb, (Associate), (MC), USNR, formerly of New York City, who entered the Medical Corps of the Navy in the very early stages of the War, was taken prisoner on Guam and was in a prisoner of war camp in Japan for more than four years, having been liberated with the coming of the American troops. He has returned to America, and at last advice was attached to St Albans Hospital in New York City

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Lieutenant Colonel Thomas H Tomlinson, F A C P, Thomasville, N C, has been awarded the Legion of Merit, with the following citation "He developed and closely supervised the theater hospitalization program and participated to a great extent in the development of all other theater medical plans. Through his untiring efforts and organizational ability he has successfully coordinated the medical activities in this theater (India-Burma) for a period of over thirty-three months"

Colonel Tomlinson is in the United States Public Health Service and has been with the executive office of the theater surgeon. He first arrived in the China-Burma-India theater in March, 1942, to help institute the first medical precautions for American forces there. He spent a part of 1942 with United States forces in the Middle East, then returned to India on permanent assignment

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A new bi-monthly medical journal, *Geriatrics*, devoted to research and clinical reports on the processes and the diseases of the aged and aging, will appear in January



under the editorship of Dr A E Hedback, who has been the editor of Modern Medicine since its inception Other journals published by Modern Medicine Publications include The Journal-Lancet and Modern Medicine

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At a recent meeting of The Maryland Association of Private Practicing Psychiatrists, Dr Wendell S Muncie, F A C P , Baltimore, Md , was elected Chairman, and Dr Horace K Richardson, F A C P , Baltimore, Md , was elected Vice-Chairman

Dr Muncie was recently elected Chairman of the new Medical Advisory Board in the reorganization plans of The Mount Hope Retreat, Baltimore, Md Dr Richardson was recently elected Secretary of Medical Advisory Board of the newly created Seton Institute in Baltimore The Seton Institute is a name selected to replace the former title of "The Mount Hope Retreat," a 600-bed psychiatric hospital

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The Institute of Medicine of Chicago conducted a conference on the control of tuberculosis in a metropolitan area, at the Palmer House, Chicago, Ill , November 13-14 Participating in the program were recognized authorities, local and national, in the field of tuberculosis, rehabilitation and public health There was also a scientific exhibit

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The American College of Radiology conducted a program and banquet commemorating the fiftieth anniversary of the discovery of x-ray, at the Palmer House, Chicago, Ill , November 8, the meeting being sponsored locally by The Chicago Roentgen Society, The Chicago Medical Society, The Institute of Medicine of Chicago and The Physics Club of Chicago

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Dr Maurice S Segal, F A C P , Assistant Professor of Medicine, Tufts College Medical School, Boston, Mass , addressed The Hartford (Connecticut) Medical Society, October 1, on "The Management of Serious Respiratory Disease with Particular Reference to Inhalational Therapy" Dr Segal also gave an address on "Penicillin Aerosol in the Management of Lobar Pneumonia, Bronchiectasis, Lung Abscess and Infective Bronchial Asthma," at the Pratt Diagnostic Hospital on October 24

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The State Medical Society of Wisconsin held its 1946 Annual Meeting at the Milwaukee Auditorium and the Schroeder Hotel, Milwaukee, October 7, 8 and 9

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Dr Joseph E Flynn (Associate) was released from the Army of the United States on October 26, 1945, to accept an assistant professorship in the Department of Pathology at Columbia University College of Physicians and Surgeons, New York City,

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Dr R H Kampmeier, F A C P , Associate Professor and Acting Director of the Department of Medicine, Vanderbilt University School of Medicine, recently returned from a 90-day tour of temporary duty with the Army in the European Theater. As a Consultant to the Office of the Surgeon General, he acted as clinician on one of the teams making surveys of the nutritional status of the civilian population in the larger cities of the American occupation zone in Germany

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The American Academy of Ophthalmology and Otolaryngology will hold its Annual Session at the Palmer House, Chicago, October 13-17, 1946

The American Academy of Allergy held its Second Annual Meeting at the Palmer House, Chicago, December 10-11, under the Presidency of Dr Oscar Swineford, Jr, F A C P, Charlottesville, Va. Numerous Fellows of The American College of Physicians appeared on the program. The American Academy of Allergy is an amalgamation of The American Association for the Study of Allergy and The Society for the Study of Asthma and Allied Conditions.

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The Michigan State Medical Society will conduct its 81st Annual Session at the Book-Cadillac Hotel, Detroit, September 25-27, 1946.

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DR ISAAC STARR ELECTED DEAN, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

Dr Isaac Starr, Professor of Therapeutics at the University of Pennsylvania School of Medicine, during November was elected dean of the School, to succeed Dr William Pepper, who is becoming dean emeritus. Dr Starr graduated from the University of Pennsylvania School of Medicine in 1920, having previously received his degree of Bachelor of Science from Princeton University. He interned at the Massachusetts General Hospital, Boston. He became an instructor in the Department of Pharmacology at the University of Pennsylvania in 1922. He became Hartzell Research Professor of Therapeutics in 1933, being the first to hold that professorship. He is widely known for developing the heart gauge, which provides information not obtainable by stethoscope or ordinary blood pressure apparatus. During the War he devoted much time to research in military medicine, and served on the National Research Council as chairman of a subcommittee on pharmacy which prepared a technical manual for the Army. He is treasurer of the College of Physicians of Philadelphia, a past president of the American Society for Clinical Investigation, a member of the Council on Pharmacy and Chemistry of the American Medical Association, and a member of the Revision Committee of the U S Pharmacopoeia. He is on the editorial board of the American Heart Journal and is a member of the Association of American Physicians, the American Association for the Advancement of Science, the American Physiological Society and the American Society of Pharmacology and Therapeutics.

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ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the Annual Meeting of the Association which will be held in Chicago, Illinois, in April or May, 1946, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, must be presented in English, and a typewritten double spaced copy sent to the corresponding Secretary, Dr T C Davison, 207 Doctors Building, Atlanta 3, Georgia, not later than February 20, 1946. The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the Annual Meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the Annual Proceedings of the Association. This will not prevent its further publication, however, in any journal selected by the author.

Dr Edward L Turner, F A C P , Bradford, Pa , has been appointed Dean of the new Medical School of the University of Washington Dr Turner graduated in medicine from the University of Pennsylvania in 1928, and for about ten years was associated with the American University of Beirut, Syria, as head of the department of physiology, head of the department of medicine and as acting dean of the medical school He returned to this country about 1938, when he accepted the presidency of the Meharry Medical College at Nashville, Tennessee, where he served as professor of medicine and head of the department until 1944

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Dr George C Dunham, F A C P , recently resigned as president of the Institute of Inter-American Affairs due to ill health However, he will continue as chairman of the Board of Directors

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Dr Stuart Graves, F A C P , University, Alabama, has become dean emeritus and professor of pathology emeritus at the Medical College of Alabama The new 4-year Medical School has already been moved to Birmingham, and Dr Roy R Kracke is the dean Dr Graves will continue some of his work in medical education, and will occupy an office in the department of biology, and act as director of admissions for the Medical College, and as an adviser to pre-medical students

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Dr C C Carpenter, F A C P , has relinquished his duties as director of the department of pathology and bacteriology at the Bowman Gray School of Medicine, Winston-Salem, because of pressure of administrative duties as dean Dr Robert P Morehead, F A C P , Wake Forest, will assume the duties as director of this department

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Colonel George M Powell, (MC), (Associate) has been made Assistant Chief Health Officer of the Panama Canal

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Dr Christopher G Parnall, F A C P , Rochester, N Y , retired on September 30 as Medical Director of the Rochester General Hospital after serving for twenty years The Acting Medical Director succeeding Dr Parnall is Dr Frank C Sutton

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Dr Walter P Anderton, F A C P , New York City, has been elected Secretary of the Medical Society of the State of New York

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Dr Bradford J Murphey, F A C P , Denver, Colo , has been elected Secretary of the Colorado State Medical Society, for a 3-year term

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Dr Thomas P Findley, Jr, F A C P , New Orleans, La , is Research Director of the Alton Ochsner Medical Foundation for research in chemistry A grant of \$5,000 was recently made to the Foundation by Smith, Kline and French, pharmaceutical manufacturers, of Philadelphia

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Major General Norman T Kirk, F A C P , Surgeon General of the United States Army, has been awarded the Distinguished Service Medal by General Somervell, Commanding General of the Army Service Forces, in recognition of his "outstanding leadership in directing the largest Medical Department in the history of the United States Army"

Brigadier General Henry C Coburn, Jr, F A C P, Post Surgeon at Fort Bragg, N C, has been retired following thirty-seven years of service with the Army. He was a native of Washington, D C, and was commissioned into the Army Medical Corps in 1908. He served in the Philippines and North China in his early Army career, and in World War I, holding the French Chevalier Legion of Honor and Victory Medal with star for his outstanding services. General Coburn was Chief of the Medical Service at Fort Sam Houston, Tex, and at Walter Reed General Hospital prior to his position of Post Surgeon at Fort Bragg.

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Brigadier General William L Hart, F A C P, Surgeon of the Eighth Service Command, will retire from active duty on December 31, 1945, concluding his thirty-seventh year of service with the United States Army Medical Department. He entered the Army Medical Corps in 1908 as a First Lieutenant, and spent several of his early years of service in the Philippines and in Mexico, and during World War I, in France and Germany. In 1940, then a Colonel, General Hart was appointed Surgeon of the Eighth Service Command, and was recently promoted to the rank of Brigadier General.

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Colonel Leon L Gardner, (MC), F A C P, formerly in charge of Public Relations and Military Intelligence, Office of the Surgeon General, has been appointed Director of the Army Medical Library.

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The following four Medical Department Colonels, recently nominated by President Truman for promotion to Brigadier Generals, have received confirmation of said promotions. William C Menninger, Director of the Neuropsychiatry Consultants Division, Office of the Surgeon General, Robert M Hardaway, F A C P, Commanding Officer of Bushnell General Hospital, Sidney L Chappell, F A C P, Commanding Officer of the England General Hospital, Edward A Noyes, F A C P, Surgeon of the Fifth Service Command.

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Dr Howard K Petry, F A C P, Harrisburg, Pa, has been elected President-Elect of the Medical Society of the State of Pennsylvania.

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*Blood—The Journal of Hematology* is a new journal to start publication in January, 1946. Dr William Dameshek, F A C P, Boston, will be the editor-in-chief. Among the associate editors will be Dr Charles A Doan, F A C P, Columbus, Dr Thomas Hale Ham, F A C P, Edgewood Arsenal, Md, and Dr Maxwell M Win-trobe, F A C P, Salt Lake City. The editorial office will be at 25 Bennett St, Boston.

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#### COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

Dr Louis N Katz, F A C P, Chicago, will direct a course in electrocardiographic interpretation for graduate physicians at the Michael Reese Hospital, Chicago, starting Wednesday, February 13, for twelve weeks, 7 00 to 9 00 p m. Further information and a copy of the program may be obtained on application to the cardiovascular department, Michael Reese Hospital.

## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

December 28—Difficulties in the Diagnosis of Surgical Lesions of the Upper Urinary Tract—Dr Leon Herman

REGION No 24 (Southern California)—Lt Comdr G C Griffith, Chairman, Capt H P Schenck, Dr J Churchill, Dr W Morrison, Maj N Nixon

*Birmingham General Hospital, Van Nuys, California*

December 26—Neuro-Surgery—Captain Everett Dickinson

*A A F Regional Station Hospital, March Field, California*

December 18—Acute Nephritis—Dr John S Lyttle

*Station Hospital, Camp Cooke, California* (afternoon session) and *Hoff General Hospital, Santa Barbara, California* (evening session)

December 19—Problems in Tuberculosis—Commanders W L Rogers and A W Hobby

*Torney General Hospital, Palm Springs, California*

December 18—Hemolytic Streptococcal Respiratory Infections and Their Sequelae—Commander Robert E Solley

*U S Naval Hospital, Santa Margarita Ranch, Oceanside, California*

December 27—Problems Associated with the Surgery of the Biliary Tract—Captain Howard K Gray

*U S Naval Hospital, Long Beach, California*

December 19—Low Back Pain—Major Samuel Weaver

*U S Naval Hospital, Corona, California*

December 27—The Use of Products of Fibrinogen and Thrombin in Otolaryngology—Captain Harry P Schenck

*U S Naval Air Training Station, San Diego, California*

December 21—The Penicillin Treatment of Syphilis and Gonorrhea—Commander W W Duemling

*A A F Regional and Convalescent Hospital, Santa Ana Army Air Base, California*

December 18—Compound Fractures—Commander P E McMasters

*OBITUARIES*

## DR MILES JOHN BREUER

Miles John Breuer, M D , F A C P , Los Angeles, Calif , died October 14, 1945, at the Veterans' Hospital at Sawtelle, Los Angeles Dr Breuer was born in Chicago, Ill , January 3, 1889, received his premedical training at the University of Texas and his medical training at Rush Medical College, Chicago, graduating in 1915, he held the degrees of B A and M S from the University of Texas, he was a member of the Phi Beta Kappa, Phi Gamma Mu, and Sigma Xi Fraternities

Dr Breuer served during the First World War at home and in France He was for many years located in Lincoln, Nebraska, but after a long illness removed to California about 1943, and for a time was located in Oakland, later moving to Los Angeles He was a member of the American Heart Association, National Tuberculosis Association, Los Angeles County, and California State Medical Societies, Fellow, American Medical Association, American Society of Clinical Pathologists, and the American College of Physicians, the latter since 1922 He was also a Diplomate of the American Board of Internal Medicine He was the author of many published papers and of a book entitled "Physiotherapy Technic "

## DR JESSE SHOUP

Jesse Shoup, B S , M D , (Associate), Washington, D C , died July 21, 1945, at Doctors Hospital at the age of 80 He resided at 200 Maryland Avenue, N E

Dr Shoup was born in 1865 near Dayton in Green County, Ohio He received the degree of Bachelor of Science from Ohio Normal University in 1888 and graduated from the Jefferson Medical College of Philadelphia in 1891 The same year he began practicing medicine in Dayton, Ohio A few years later, 1894, he secured his license to practice in the District of Columbia and continued to serve the District as a general practitioner for half a century He had held staff appointments at Providence, Sibley and Garfield Hospitals

He was a member of the old American Congress on Internal Medicine, and by virtue thereof became an Associate of the American College of Physicians in 1926, when the Congress was merged with the College

Dr Shoup had been affiliated with both the Medical Association of the District of Columbia and the Medical Society of the District of Columbia, becoming a member of the former in 1896 and of the latter in 1902 He had been a Life Member since 1937

He was a Fellow of the American Medical Association, a member of the Washington Heart Association, and a charter member of the Washington Medical and Surgical Society

His wife, Mrs Anna Shoup, survives him, together with a brother, Arthur A Shoup, and a sister, Miss Olive Shoup, both of Dayton, Ohio  
 WALLACE M YATER, M D , F A C P ,  
 Governor for the District of Columbia

### DR PAUL BROWN WELCH

Paul Brown Welch, M D , F A C P , Miami, Florida, died May 6, 1945 Dr Welch was born November 23, 1889, at Wauneta, Kansas He was a graduate of the University of Illinois and became nationally known in his specialty of Gastroenterology He was the author of numerous and important papers pertinent to his field and was recognized as one of the leading specialists in the South He had been Chief of the Gastroenterological service at Jackson Memorial Hospital since 1934 During his many years of residence in that area he became widely and favorably regarded, not alone for his unusual talents but also because of his personal charm and his universal liking for patients, friends, and colleagues His untimely demise will long be regretted by those who knew him well and were privileged to enjoy his friendship

C FREDERIC ROCHE, M D , F A C P

### DR KENDAL FROST

Dr Kendal Frost, for many years one of the foremost dermatologists on the Pacific Coast, died on September 28, 1945, at his home in Los Angeles, California

Dr Frost was a member of a pioneer Los Angeles family, he was a graduate of the University of California and of Rush Medical College He later studied in Paris and after serving as an officer in World War I he acted as a member of Herbert Hoover's Belgian Relief Commission Returning to California after the war he early decided to specialize in dermatology and syphilology and from then on rose steadily until at the time of his death he had been prominent in practically all work connected with his specialty

For many years he was Clinical Professor of Medicine (Dermatology and Syphilology), at the University of Southern California, and Chairman of this department at the Los Angeles General Hospital; he was a member of the American Medical Association, the American Dermatological Association, the California Medical Association, the Los Angeles County Medical Society, Los Angeles Academy of Medicine, the Los Angeles Dermatological Society and the Los Angeles Symposium Society, on the staff of the Hospital of the Good Samaritan and of St Vincent's Hospital and Consulting Dermatologist for the Children's Hospital and the Santa Fe Hospital He also was a member of the Los Angeles Museum Patron's Association, the California Club and Theta Delta Chi Fraternity

Dr Frost was a man of high moral character, particularly high standards, and outstanding in his field, he will be greatly missed by all members of the profession in Los Angeles. He is survived by his widow, one son, Kendal, Jr and one daughter, Rebecca.

ROY E. THOMAS, M.D., F.A.C.P.,  
Governor for Southern California

### DR. GEORGE ARGALE HARROP

Dr. George Argale Harrop died of heart disease on August 4, 1945, at the Presbyterian Hospital, New York City.

Dr. Harrop was born in Peru, Illinois, in 1891, attended Harvard (A.B., 1912) and Johns Hopkins (M.D., 1916). He did his postgraduate work at the University of Copenhagen, and then after a short period at the College of Physicians and Surgeons of Columbia University was called to assist in the organization of medical science at the Peking Union Medical College. Returning from China in 1924, he was appointed Assistant Professor of Medicine at Hopkins and Associate Physician in the Johns Hopkins Hospital. He was here from 1925 to 1937 and largely concerned with research on metabolism and endocrinology.

When the Squibbs Institute for Medical Research was founded in 1937 Dr. Harrop was appointed Director of Research, and in 1943 was elected a vice-president of the company. On taking up his work with the Institute he moved to Princeton and in 1938 received an appointment from Princeton University as lecturer in biology.

At the Squibbs Institute Dr. Harrop had much to do with large scale production of penicillin, as well as directing research in malaria, the treatment of shock, and other problems. At the University his research was on fundamental problems of mammalian physiology, beyond which he was always ready to encourage and help staff members and advanced students. He had established a real place among the Princeton faculty, and one of his fellow faculty members said of him "He was a brilliant investigator and, withal, a fine and cultured gentleman. He will be keenly missed as a member of Princeton's scientific community."

Dr. Harrop also served as Medical Consultant to the Middlesex General Hospital, New Brunswick, he was a Diplomate, American Board of Internal Medicine, Fellow, since 1931, of the American College of Physicians, Fellow, the American Scandinavian Foundation, Member, American Society of Biological Chemists, Society for Experimental Biology and Medicine, New York Academy of Medicine, American Clinical and Climatological Association, and Societe Biologique of Paris. He was the author of "Management of Diabetes" 1925, and "Diet in Disease" 1930, as well as numerous articles on metabolism and dietetics.

Surviving are his wife, Mrs. Esther Caldwell Harrop, three sons, George



Argale Harrop 3d, William Caldwell and David Cole Harrop, and a daughter Esther Harrop

GEORGE H. LATHROPE, M D , F A C P ,  
Governor for New Jersey

### DR WILLIAM A Groat

William Avery Groat, M D , F A C P , Syracuse, N Y Born, Canastota, N Y , 1876, M D Syracuse University College of Medicine, 1900, for many years, Professor of Clinical Pathology at his alma mater and a Trustee of the University, Senior Attending Physician and Director, Hazard Memorial Laboratory, Syracuse Memorial Hospital, Senior Attending Physician, Diseases of Metabolism, and Director of the Jacobson Memorial Laboratory, St Joseph Hospital, Consultant, University, City and Syracuse Psychopathic Hospitals, Chairman, Advisory Committee on Public Health, City of Syracuse, Former President, Medical Society of the State of New York and Syracuse Academy of Medicine, member of the House of Delegates, American Medical Association, 1939, 1940 and 1942; member, American Association of Immunologists, American Association for the Study of Gonorrhea, American Society of Clinical Pathologists and the Association for the Study of Internal Secretions, Diplomate, American Board of Internal Medicine, Fellow of the American College of Physicians since 1926, served during World War I, Lt Col , Medical Officers Reserve Corps, at the time of his death, member of the Management Committee of the New York State Journal of Medicine, died September 9, 1945, aged 68, of chronic myocarditis and cerebral arteriosclerosis

In addition to the above he was a member of two Medical clubs in Syracuse, N Y , i e the Thursday night Club and the Hiawatha Club

Dr Groat's major interest in Internal Medicine was hematology and metabolic diseases. He was the first one in Syracuse to carry out the Wassermann reaction and for several years before the New York State laboratories undertook their routine performance Dr Groat made many such tests for the physicians in Syracuse and the surrounding territory. He rendered very valuable service to the physicians in the community. He made several original observations in hematology and metabolic diseases which were reported in the literature.

Dr Groat had a scientific, inquiring mind. He was greatly admired by his friends and patients. He was frequently consulted on problems in hematology and metabolic diseases by physicians in Central, Northern and Southern New York who regarded his opinion very highly.

At the death of Dr Groat Syracuse lost one of its most valuable physicians.

EDWARD C. REILINSTEIN, M D , F A C P ,  
Syracuse, N Y

## COLONEL THOMAS WARD BURNETT

Thomas Ward Burnett, M D , F A C P , died suddenly on October 19, 1945 Colonel Burnett retired from the Medical Corps of the regular Army on June 30, 1945, and since that time had been residing at the Hotel Henry Hudson in New York City

Colonel Burnett was born at Summit, New York, in 1882 He attended Wesleyan University for three years, and graduated in medicine from Columbia University College of Physicians and Surgeons in 1908 He was a resident intern at the New York Hospital, 1908-10, and thereafter practiced medicine and engaged in hospital work at White Plains, New York, for a year He entered the Medical Corps of the United States Army and studied at the Army Medical School in Washington, D C His career was devoted to the usual assignments of a medical officer in the Army, he filled assignments at Army posts in various parts of the United States and at Army installations in the Pacific

He was the author of a considerable number of publications appearing in various medical journals He was a member of the Association of Military Surgeons of the United States, an honorary member of the American Medical Association, and had been a Fellow of the American College of Physicians since 1936

He was a genial gentleman, was possessed of broad interests and much enthusiasm He exhibited an active interest in medical progress and was at all times an enthusiastic Fellow of the College

## DR BEVERLEY RANDOLPH TUCKER

Dr Beverley Randolph Tucker of Richmond, Virginia, was born on April 26, 1874 He received his academic education at the Virginia Military Institute and later received the Degree of Doctor of Medicine at the Medical College of Virginia in 1905 An internship followed in 1905-1906 at the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia Subsequently, Dr Tucker engaged in postgraduate work at Ward's Island, New York, and still later at the Allgemeines Krankenhaus, Vienna Early in his training he determined upon the special study of Neuropsychiatry and practiced this branch of medicine with skill and distinction up to the time of his death

Numerous distinctions, honors, and professional associations attended Dr Tucker's career He was Chief of Staff of the Tucker Sanatorium, Consulting Neuropsychiatrist at the Johnston-Willis and St Elizabeth's Hospitals, a member of the Medical Advisory Board, Virginia Selective Service, past President of the Tri-State Medical Association and the Mental Hygiene Society of Virginia, President from 1942-1943 of the Richmond Academy of Medicine, a member of the American Neurological Association and the American Psychiatric Association, a Fellow of the American Medi-

al Association and the American College of Physicians, the latter since 1920. He was also a member of the Society of Cincinnati, having served as President in the State of Virginia from 1933-1935. He was a member of the State Board of Health and contributed wisely to many of the problems confronting this body. During World War I, he was a member of the Medical Advisory Board in Virginia and Contract Surgeon in the U S Army. At one time, he was Vice Chairman of the City Library Board of Richmond, first Juvenile Court Physician, a founder of the Children's Clinic, and held numerous other positions of responsibility and distinction. In 1938, he became Emeritus Professor of Neuropsychiatry of the Medical College of Virginia.

Dr. Tucker was a scholar of ability and action. His writings were not limited to the field of medicine but he was active in this field. He was interested particularly in the education of young men and constantly strove to stimulate them to investigative work. His own investigations occupied a good deal of his time and he was constantly working on some problem. Disinclined to think along orthodox lines, he stirred up considerable discussion with his work on pellagra and a discussion of the effect of this disease on mental disorders. Studies on the pituitary gland and the hypothalamus were also contributed.

In addition to his medical writings, Dr. Tucker entered other literary fields and was the author of "S. Wier Mitchell" (1914), "Verses of Virginia" (1923), "The Gift of Genius" (1930), a novel, "Narna Dariell" (1936), and "Tales of the Tuckers" (1942). Other medical writings included editorials as editor of the "Old Dominion Journal of Medicine and Surgery", the section on Cranial Nerves in Tice's Practice of Medicine, and numerous other articles.

Dr. Beverley Tucker was a gracious host and enjoyed entertaining his friends. His interest in the Confederacy was one of his strong characteristics. He, no doubt, fought and re-fought the conflict of 1861 up to the time of his death and, like many Southern gentlemen of his time, was largely unreconstructed. He had many other interesting qualities, one of which was his essential disregard of ill health as, during the last four or five years of his life, he had numerous episodes representing relatively marked disability. However, he ignored these and continued at his desk with his work. Many of his friends found it amusing that he felt that exercise was a waste of time and rarely, if ever, did he indulge in any sport or games, spending most of his time in working on medicine or some literary pursuit. Beverley Randolph Tucker, founder of the Tucker Hospital, died in this institution on June 19, 1945.

J. EDWIN WOOD, M.D., F.A.C.P.,  
Governor for Virginia

# ANNALS OF INTERNAL MEDICINE

## AUTHOR INDEX

Volume 23, July-December, 1945

- |   |     |  |     |
|---|-----|--|-----|
| AIKAWA, J K Hypersensitivity and Rheumatic Fever Part I   | 969 | Report of Cases Treated without Anti-coagulant Agents  | 491 |
| Part II Relation of Rheumatic Fever to Hypersensitivity   | 983 | BLANKENHORN, M A The Diagnosis of Beriberi Heart Disease   | 398 |
| ALPERS, B J, H E YASKIN and — Neuropsychiatric Complications Following Spinal Anesthesia  | 184 | BLECKWENN, W J Neuroses in the Combat Zone   | 177 |
| ANDERSON, R G, E M CHAPMAN and — Aids in Physical Diagnosis Signs over the Lower Left Lung Caused Chiefly by Cardiac Enlargement  | 35  | BLOUNT, S G, JR and J T BARRETT Acute Lupus Erythematosus Disseminatus A Report of a Case in a Male with Associated Atypical Verrucous Endocarditis (Libman-Sacks) <i>Case Rep</i> | 251 |
| APPLEBAUM, I L, J SHRAGER and W PAFF Lymphocytosis in the Cerebrospinal Fluid   | 158 | BOENHEIM, F, D SCHWIMMER and T H MCGAVACK The Combination of Hyperthyroidism and Pernicious Anemia Report of a Case with a Review of the Literature <i>Case Rep</i>                | 869 |
| ARNOLD, H L, JR and I L TILDEN The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both   | 65  | BOHARAS, S and L H CRIEP Interlobar Effusion Associated with Congestive Heart Failure <i>Case Rep</i>  | 426 |
| ASHLEY, J D, JR, W LANGSTON, O A WHITE and — Splenic Neutropenia Report of a Case with Splenectomy <i>Case Rep</i>  | 667 | CANDEL, S and M C WHELOCK Acute Non-Specific Myocarditis   | 309 |
| BABKIN, B P Secretory Mechanisms of the Digestive Glands <i>Rev</i>   | 449 | CASALS, J A Current View of the Rabies Problem   | 74  |
| BARR, D P and E SHORR Observations on the Treatment of Graves' Disease with Thiouracil  | 754 | CHAPMAN, E M and R G ANDERSON Aids in Physical Diagnosis Signs over the Lower Left Lung Caused Chiefly by Cardiac Enlargement  | 35  |
| BARRETT, J T, S G BLOUNT, JR and — Acute Lupus Erythematosus Disseminatus A Report of a Case in a Male with Associated Atypical Verrucous Endocarditis (Libman-Sacks) <i>Case Rep</i> | 251 | CHUSID, J G and G H MARQUARDT Acute Infectious Polyneuritis (Guillain-Barre Type) -  | 852 |
| BEN-ASHER, S Hypertension Caused by Renal Infarction <i>Case Rep</i>  | 431 | CLERF, L H, J R FOX and — Broncholithiasis Report of 10 Cases  | 955 |
| BENOIT, M, W McDERMOTT, M M LEASK and — <i>Streptobacillus moniliformis</i> as a Cause of Subacute Bacterial Endocarditis Report of a Case Treated with Penicillin <i>Case Rep</i>    | 414 | COE, G C Primary Bronchopulmonary Aspergillosis, An Occupational Disease <i>Case Rep</i>   | 423 |
| BERCOVITZ, Z T Malaria Complicated by Pneumonia, Treatment with Sulfadiazine and Atabrine <i>Case Rep</i>   | 79  | COHEN, M, J W SHIRER and — The Effects of Thiouracil on the Thyroid Gland  | 790 |
| BLAKE, F G, J R GOERNER, A J GEIGER and — Treatment of Subacute Bacterial Endocarditis with Penicillin  |     | CRANE, A R and A M ZETLIN Hemolytic Anemia, Hyperglobulinemia and Boeck's Sarcoid <i>Case Rep</i>  | 882 |
|   |     | CRELLIN, J A, H J F KULLMAN and — Penicillin in Suppurative Disease of the Lungs Due to <i>Streptococcus hemolyticus</i>   | 135 |

- CRIEF, L H, S BOHARAS and — Inter-  
lobar Effusion Associated with Conges-  
tive Heart Failure *Case Rep* 426
- D'ALBORA, J B, J N. EDSON, A. P IN-  
GEGNO and — Amebiasis A Report  
of 39 Cases Observed in an Army Gen-  
eral Hospital Stationed in Northern  
Ireland 960
- DANOWSKI, T S, A W WINKLER and J  
P PETERS Tissue Calcification and  
Renal Failure Produced by Massive  
Dose Vitamin D Therapy of Arthritis 22
- DAY, K M Diagnosis and Surgical  
Treatment of Ménière's Disease (Hy-  
drops of Labyrinth) 41
- DOWLING, H F, L K SWEET, E  
DUMOFF-STANLEY and — Meningo-  
coccic Meningitis Treated with Sulfadiazine and Sulfamerazine A Three-  
Year Study 338
- DRFY, N W and F B QUEEN Follicu-  
lar Lymphoma (Brill-Symmers Dis-  
ease) Unsuccessfully Treated with Pen-  
icillin *Case Rep* 1009
- DUMOFF-STANLEY, E, L K SWEET, —  
and H F DOWLING Meningococcic  
Meningitis Treated with Sulfadiazine  
and Sulfamerazine A Three-Year  
Study 338
- LECKI, R S, A YIOMANS, J C SNYDER,  
E S MURRAY, — and C J D ZARA-  
TONLIS Azotemia in Typhus Fever 711
- EDSON, J N, A P INGEGNO and J B  
D'ALBORA Amebiasis A Report of  
39 Cases Observed in an Army General  
Hospital Stationed in Northern Ireland 960
- EICHLER, B B and S N HILLER An-  
eurysm of Aorta with Compression of  
Pulmonary Artery and Left Auricle  
*Case Rep* 652
- FISCHER, I, A C OSMAN and — Men-  
ingococcic Infections with Special Ref-  
erence to Certain Diagnostic Considera-  
tions, An Analysis of Thirty-Seven  
Cases 924
- FOX, J R and L H CLIFFE Broncho-  
pneumonia Report of 10 Cases 955
- FRANKLIN, J Spontaneous Hemopneu-  
mothorax Report of a Case Occurring  
in a Soldier *Case Rep* 437
- GABRILOVE, J L, M J KERT and L J  
SOFFER The Use of Thiouracil in the  
Treatment of Patients with Hyper-  
thyroidism 537
- GAY, L N The Integration of the Exact  
Sciences in Allergy Research 53
- GEIGER, A J, J R GOERNER, — and F  
G BLAKE Treatment of Subacute  
Bacterial Endocarditis with Penicillin  
Report of Cases Treated without Anti-  
coagulant Agents 491
- GLASSBURN, E M, P S STRONG and —  
Thrombocytopenic Purpura Following  
the Use of Sulfathiazole *Case Rep* 237
- GLASSER, O, E H QUIMBY, L S TAYLOR  
and J L WEATHERWAY Physical  
Foundations of Radiology *Rev* 111
- GOERNER, J R, A J GEIGER and F G  
BLAKE Treatment of Subacute Bac-  
terial Endocarditis with Penicillin Re-  
port of Cases Treated without Antico-  
agulant Agents 491
- GOLDEN, R Radiologic Examination of  
the Small Intestine *Rev* 280
- GOODMAN, A A, E. M WEINBERGER, S  
W LIPPINCOTT, A MARBLE and W H  
WRIGHT Studies of Filariasis in Sol-  
diers Evacuated from the South Pacific 823
- GREENE, J A The Syndrome of Psoas  
Myositis and Fibrositis, Its Manifesta-  
tions and Its Significance in the Differ-  
ential Diagnosis of Lower Abdominal  
Pain 30
- HARRIS, W H, JR Upper Respiratory  
Infections A Résumé of Recent Pertu-  
nent Data and Observations of Inci-  
dence Aboard a Destroyer 147
- HATCH, F N Atrophic Arthritis Asso-  
ciated with Splenomegaly and Leuko-  
penia 201
- HILLER, S N, B B EICHLER and —  
Aneurysm of Aorta with Compression  
of Pulmonary Artery and Left Auricle  
*Case Rep* 652
- HOLT, R A, J P LANCET and — Pul-  
monary Actinomycosis Due to *Actino-  
myces gramineus* *Case Rep* 91
- INGEGNO, A P, J N EDSON, — and J B  
D'ALBORA Amebiasis A Report of  
39 Cases Observed in an Army General  
Hospital Stationed in Northern Ire-  
land 960

- JOSEY, A I, J W TRENIS and W F KAMMER Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, Penicillin and Repeated Thoracenteses 800
- JOSEY, A I, W E LEEDE and — The Early Diagnosis of Filariasis and Certain Suggestions Relative to Cause of Symptoms 816
- KAMMER, W F, A I JOSEY, J W TRENIS and — Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, Penicillin and Repeated Thoracenteses 800
- KATTWINKEL, E E Back Pain as a Symptom of Carcinoma of the Body of the Pancreas *Case Rep* 1006
- KAUVAR, S, R W MOODY and — The Use of Penicillin in Agranulocytosis *Case Rep* 1015
- KERT, M J, J L GABRILOVE, — and L J SOFFER The Use of Thiouracil in the Treatment of Patients with Hyperthyroidism 537
- KLEIN, C, G SALAND, R ROSENTHAL, — and H ZURROW The Effect of Doryl (Carbaminoylcholine) in the Treatment of Peripheral Vascular Disease 48
- KOLMER, J A Penicillin Therapy Including Tyrothricin and Other Antibiotic Therapy *Rev* 449
- KRUGER, A L, A W WALLACE and S J PENCHANSKY Infectious Mononucleosis A Clinical Study of Sixty-Three Cases 945
- KUGEL, V H and M A SCHNITKER The Value of Penicillin in the Control of Sepsis Complicating a Case of Severe Granulocytopenia (Aleukemic Leukemia) *Case Rep* 1001
- KULLMAN, H J F and J A CRELLIN Penicillin in Suppurative Disease of the Lungs Due to *Streptococcus hemolyticus* 135
- LANGSTON, W, O A WHITE and J D ASHLEY, JR Splenic Neutropenia Report of a Case with Splenectomy *Case Rep* 667
- LEASK, M M, W McDERMOTT, — and M BENOIT *Streptobacillus moniliformis* as a Cause of Subacute Bacterial Endocarditis Report of a Case Treated with Penicillin *Case Rep* 414
- LEEDE, W E and A I JOSEY The Early Diagnosis of Filariasis and Certain Suggestions Relative to Cause of Symptoms 816
- LIPPINCOTT, S W, A A GOODMAN, E M WEINBERGER, — A MARBLE and W H WRIGHT Studies of Filariasis in Soldiers Evacuated from the South Pacific 823
- LITTLE, A G, JR, M H POWER and E G WAKEFIELD Absorption and Excretion of Iron 627
- LYMAN, R A, EDITOR American Pharmacy *Rev* 1023
- LYNCH, J P and R A HOLT Pulmonary Actinomycosis Due to *Actinomyces graminis* *Case Rep* 91
- MANCHESTER, R C Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria 935
- MANCUSI-UNGARO, L Familial Myasthenia Gravis *Case Rep* 249
- MARBLE, A, A A GOODMAN, E M WEINBERGER, S W LIPPINCOTT, — and W H WRIGHT Studies of Filariasis in Soldiers Evacuated from the South Pacific 823
- MARPLE, C D Progressive (Disseminated) Coccidioidomycosis *Case Rep* 240
- MARQUARDT, G H, J G CHUSID and — Acute Infectious Polyneuritis (Guillain-Barré Type) 852
- McARTHUR, J W, R W RAWSON and J H MEANS Idiosyncratic Febrile Reactions to Thiouracil Clinical Characteristics and Possible Pharmacologic Significance 915
- McDERMOTT, W, M M LEASK and M BENOIT *Streptobacillus moniliformis* as a Cause of Subacute Bacterial Endocarditis Report of a Case Treated with Penicillin *Case Rep* 414
- McGAVACK, T H, F BOENHEIM, D SCHWIMMER and — The Combination of Hyperthyroidism and Pernicious Anemia Report of a Case with a Review of the Literature *Case Rep* 869
- McINTYRE, D W, C D MILLER and — A Syndrome Termed Reiter's Disease (Urethritis, Conjunctivitis and Arthritis) *Case Rep* 673
- McKINNON, J, O SWINEFORD, JR and — Multiple Fractures of Ribs by Cough *Case Rep* 442

- MEANS, J H Hyperophthalmopathic Graves' Disease 779
- MEANS, J H, J W McARTHUR, R W RAWSON and — Idiosyncratic Febrile Reactions to Thiouracil Clinical Characteristics and Possible Pharmacologic Significance 915
- MILLER, C D and D W McINTYRE A Syndrome Termed Reiter's Disease (Urethritis, Conjunctivitis and Arthritis) *Case Rep* 673
- MOODY, R W and S KAUFAR The Use of Penicillin in Agranulocytosis *Case Rep* 1015
- MOUITON, F R, EDITOR. The Chemistry and Physiology of the Hormones *Rev* 687
- MURPHY, R C, JR and S SHAPIRO The Pathology of Sickle Cell Disease 376
- MURRAY, E S, A YEOMANS, J C SNYDER, — R S ECKE and C J D ZARAFONETIS Azotemia in Typhus Fever 711
- NATHANSON, L, B SELIGMAN and — "Metastatic" Calcification in Soft Tissues of Legs in Osteitis Deformans *Case Rep* 82
- NORWOOD, W F Medical Education in the United States before the Civil War *Rev* 893
- OXMAN, A C and I FISCHER Meningococcal Infections with Special Reference to Certain Diagnostic Considerations, An Analysis of Thirty-Seven Cases 924
- PARR, W, I L APPLI BAUM, J SHRAGER and — Lymphocytosis in the Cerebrospinal Fluid 170
- PAPSON, G W. Dextrocardia with Situs Inversus Complicated by Chronic Rheumatic Aortic and Mitral Endocarditis *Case Rep* 102
- PINCHANSKY, S J, A L KRUGER, A W WALLACE and — Infectious Mononucleosis: A Clinical Study of Sixty-Three Cases 915
- PETERS, J P, T S DANOWSKI, A W WINKLER and — Tissue Calcification and Renal Failure Produced by Massive Dos Vitamin D Therapy of Arthritis 22
- PETERS, J T. Equine Infectious Anemia transmitted to Man *Case Rep* 271
- PETERS, J. T. Oliguria and Anuria Due to Increased Intrarenal Pressure . 221
- POWER, M H, A G LITTLE, JR, — and E G WAKEFIELD Absorption and Excretion of Iron 627
- PULLEN, R L, B M STUART and — Endemic (Murine) Typhus Fever Clinical Observations of 180 Cases 520
- QUEEN, F B, N W DREY and — Follicular Lymphoma (Brill-Symmers Disease) Successfully Treated with Penicillin *Case Rep* 1009
- QUEEN, F B, R W ROBINSON and — Isolated (Fiedler's) Myocarditis Report of Case First Manifested by Arterial Emboli in Extremities and Terminally by Mural Thrombi in Three of the Heart Chambers *Case Rep* 860
- QUIMBY, E H, O GLASSER, — L S TAYLOR and J L WEATHERWAX Physical Foundations of Radiology *Rev* 111
- RAWSON, R W, J W McARTHUR, — and J H MEANS Idiosyncratic Febrile Reactions to Thiouracil Clinical Characteristics and Possible Pharmacologic Significance 915
- ROBINSON, R W and F B. QUEEN Isolated (Fiedler's) Myocarditis Report of Case First Manifested by Arterial Emboli in Extremities and Terminally by Mural Thrombi in Three of the Heart Chambers *Case Rep* 860
- ROSENTHAL, R, G SALAND, — C KLEIN and H ZURROW The Effect of Doryl (Carbaminoylecholine) in the Treatment of Peripheral Vascular Disease 48
- ROTHENDLER, H H Comparative Electrocardiographic Changes in Angina Pectoris and Coronary Thrombosis in the Same Patient *Case Rep* 268
- SACKS, D R Case Report of Dissecting Aneurysm of the Aorta with Cardiac Tamponade *Case Rep* 661
- SALAND, G, R ROSENTHAL, C KLEIN and H ZUPROW The Effect of Doryl (Carbaminoylecholine) in the Treatment of Peripheral Vascular Disease 48
- SCHNITKER, M A, V H KUGEL and — The Value of Penicillin in the Control of Sepsis Complicating a Case of Severe

- Granulocytopenia (Aleukemic Leukemia) *Case Rep* 1001
- SCHWIMMER, D, F BOENHEIM, — and T H MCGAVACK The Combination of Hyperthyroidism and Pernicious Anemia Report of a Case with a Review of the Literature *Case Rep* 869
- SELIGMAN, B and L NATHANSON "Metastatic" Calcification in Soft Tissues of Legs in Osteitis Deformans *Case Rep* 82
- SHAPIRO, S, R C MURPHY, JR and — The Pathology of Sickle Cell Disease 376
- SHIRER, J W and M COHEN The Effects of Thiouracil on the Thyroid Gland 790
- SHORR, E, D P BARR and — Observations on the Treatment of Graves' Disease with Thiouracil 754
- SHRAGER, J, I L APPELBAUM, — and W PAFF Lymphocytosis in the Cerebrospinal Fluid 170
- SIEGAL, S Benign Paroxysmal Peritonitis 1
- SNYDER, J C, A YEOMANS, — E S MURRAY, R S ECKE and C J D ZARAFONETIS Azotemia in Typhus Fever 711
- SOFFER, L J, J L GABRILOVE, M J KERT and — The Use of Thiouracil in the Treatment of Patients with Hyperthyroidism 537
- STRONG, P S and E M GLASSBURN Thrombocytopenic Purpura Following the Use of Sulfathiazole *Case Rep* 237
- STUART, B M and R L PULLEY Endemic (Murine) Typhus Fever Clinical Observations of 180 Cases 520
- SWEET, L K, E DUMOFF-STANLEY and H F DOWLING Meningococcal Meningitis Treated with Sulfadiazine and Sulfamerazine A Three-Year Study 338
- SWINEFORD, O, JR and J MCKINNON Multiple Fractures of Ribs by Cough *Case Rep* 442
- TAYLOR, L S, O GLASSER, E H QUIMBY, — and J L WEATHERWAX Physical Foundations of Radiology *Rev* 111
- THANNHAUSER, S J Werner's Syndrome (Progeria of the Adult) with Rothmund's Syndrome, Two Types of Closely Related Heredofamilial Atrophic Dermatoses with Juvenile Cataracts and Endocrine Features, A Critical Study with Five New Cases 559
- THIENES, C H Fundamentals of Pharmacology *Rev* 111
- THOMAS, J W, H S VAN ORDSTRAND and C TOMLINSON The Treatment of Bronchiectasis with Chemotherapy and Allergy Management 405
- TICE, G M The Unusual in Gastrointestinal Roentgenology 837
- TILDEN, I L, H L ARNOLD, JR and — The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both 65
- TOMLINSON, C, J W THOMAS, H S VAN ORDSTRAND and — The Treatment of Bronchiectasis with Chemotherapy and Allergy Management 405
- TRENIS, J W, A I JOSEY, — and W F KAMMER Treatment of Postpneumonia Thoracic Empyema with Sulfonamides, Penicillin and Repeated Thoracenteses 800
- VAN ORDSTRAND, H S, J W THOMAS, — and C TOMLINSON The Treatment of Bronchiectasis with Chemotherapy and Allergy Management 405
- WAKEFIELD, E G, A G LITTLE, JR, M H POWER and — Absorption and Excretion of Iron 627
- WALLACE, A W, A L KRUGER, — and S J PENCHANSKY Infectious Mononucleosis A Clinical Study of Sixty-Three Cases 945
- WARNER, E C, EDITOR Savill's System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease for Students and Practitioners *Rev* 280
- WEINBERGER, E M, A A GOODMAN, — S W LIPPINCOTT, A MARBLE and W H WRIGHT Studies of Filariasis in Soldiers Evacuated from the South Pacific 823
- WEISS, A, F M WILLETT and — Coccidioidomycosis in Southern California Report of a New Endemic Area with a Review of 100 Cases 349
- WHELOCK, M C, S CANDEL and — Acute Non-Specific Myocarditis 309
- WHITE, O A, W LANGSTON, — and J D ASHLEY, JR Splenic Neutropenia



- Report of a Case with Splenectomy  
*Case Rep* 667
- WIGGERS, C J The Functional Consequences of Coronary Occlusion 158
- WILLETT, F M and A WEISS Coccidioidomycosis in Southern California Report of a New Endemic Area with a Review of 100 Cases 349
- WINKLER, A W, T S DANOWSKI, — and J P PETERS Tissue Calcification and Renal Failure Produced by Massive Dose Vitamin D Therapy of Arthritis 22
- WOLF, G A, JR Mechanism of Reflex Anuria *Case Rep* 99
- WRIGHT, W H, A A GOODMAN, E M WEINBERGER, S W LIPPINCOTT, A MARBLE and — Studies of Filariasis in Soldiers Evacuated from the South Pacific 823
- YASKIN, H. E and B J ALPERS Neuropsychiatric Complications Following Spinal Anesthesia 184
- YEOMANS, A, J C SNYDER, E S MURRAY, R S ECKE and C J D ZARAFONETIS Azotemia in Typhus Fever 711
- ZARAFONETIS, C J D, A YEOMANS, J C SNYDER, E S MURRAY, R S ECKE and — Azotemia in Typhus Fever 711
- ZETLIN, A M, A R CRANE and — Hemolytic Anemia, Hyperglobulinemia and Boeck's Sarcoid *Case Rep* 882
- ZIMMERMAN, S L Ventricular Tachycardia—a Report of 10 Cases, Eight of Which Were Treated with Quinidine with Recovery in Seven 634
- ZURROW, H, G SALAND, R ROSENTHAL, C KLEIN and — The Effect of Doryl (Carbaminoylcholine) in the Treatment of Peripheral Vascular Disease 48

# ANNALS OF INTERNAL MEDICINE

## SUBJECT INDEX

Volume 23, July-December, 1945

- A**CTINOMYCOSIS, Pulmonary —  
 Due to *Actinomyces graminis* J P LYNCH and R A HOLT *Case Rep* 91
- AGranulocytosis, The Use of Penicillin in — R W MOODY and S KAUFAR *Case Rep* 1015
- Allergy Research, The Integration of the Exact Sciences in — L N GAY 53
- Amebiasis A Report of 39 Cases Observed in an Army General Hospital Stationed in Northern Ireland J W EDSON, A P INGEGNO and J B D'ALBORA 960
- Anemia, Chronic Hemolytic — with Paroxysmal Nocturnal Hemoglobinuria R C MANCHESTER 935
- Anemia, Equine Infectious — Transmitted to Man J T PETERS *Case Rep* 271
- Anemia, Hemolytic —, Hyperglobulinemia and Boeck's Sarcoid A R CRANE and A M ZETLIN *Case Rep* 882
- Anemia, Mediterranean — *Edit* 683
- Anemia, The Combination of Hyperthyroidism and Pernicious — Report of a Case with a Review of the Literature F BOENHEIM, D SCHWIMMER and T H MCGAVACK *Case Rep* 869
- Anesthesia, Neuropsychiatric Complications Following Spinal — H E YASKIN and B J ALPERS 184
- Aneurysm, Case Report of Dissecting — of the Aorta with Cardiac Tamponade D R SACKS *Case Rep* 661
- Aneurysm of Aorta with Compression of Pulmonary Artery and Left Auricle B B EICHLER and S N HELLER *Case Rep* 652
- Angina Pectoris and Coronary Thrombosis in the Same Patient, Comparative Electrocardiographic Changes in — H H ROTHENDLER *Case Rep* 268
- Anuria, Mechanism of Reflex — G A WOLF, JR *Case Rep* 99
- Anuria, Oliguria and — Due to Increased Intrarenal Pressure J T PETERS 221
- Arthritis, Atrophic — Associated with Splenomegaly and Leukopenia F N HATCH 201
- Arthritis, Tissue Calcification and Renal Failure Produced by Massive Dose Vitamin D Therapy of — T S DANOWSKI, A W WINKLER and J P PETERS 22
- Aspergillosis, Primary Bronchopulmonary —, An Occupational Disease G C COE *Case Rep* 423
- Atabrine, Treatment with Sulfadiazine and — Malaria Complicated by Pneumonia — Z T BERCOVITZ *Case Rep* 79
- Azotemia in Typhus Fever A YEOMANS, J C SNYDER, E S MURRAY, R S ECKE and C J D ZARAFONETIS 711
- B**ACK Pain as a Symptom of Carcinoma of the Body of the Pancreas E E KATTWINKEL *Case Rep* 1006
- Bacterial Endocarditis, *Streptobacillus moniliformis* as a Cause of Subacute — Report of a Case Treated with Penicillin W McDERMOTT, M M LEASK and M BENOIT *Case Rep* 414
- Bacterial Endocarditis, Treatment of Subacute — with Penicillin Report of Cases Treated without Anticoagulant Agents J R GOERNER, A J GEIGER and F G BLAKE 491
- Beriberi Heart Disease, The Diagnosis of — M A BLANKENHORN 398
- Bronchiectasis, The Treatment of — with Chemotherapy and Allergy Management J W THOMAS, H S VAN ORSTRAND and C TOMLINSON 405
- Broncholithiasis Report of 10 Cases J R FOX and L H CLERF 955
- Bronchopulmonary Aspergillosis, Primary —, An Occupational Disease G C COE *Case Rep* 423
- C**ALCIFICATION, "Metastatic" — in Soft Tissues of Legs in Osteitis Deformans B SELIGMAN and L NATHANSON *Case Rep* 82

- Calcification, Tissue — and Renal Failure Produced by Massive Dose Vitamin D Therapy of Arthritis T S DANOWSKI, A W WINKLER and J P PETERS 22
- Carcinoma of the Body of the Pancreas, Back Pain as a Symptom of — E E KATTWINKEL *Case Rep* 1006
- Chemistry and Physiology of the Hormones, The —. F. R. MOULTON, Editor *Rev* 687
- Coccidioidomycosis in Southern California Report of a New Endemic Area with a Review of 100 Cases F M WILLETT and A WEISS 349
- Coccidioidomycosis, Progressive (Disseminated) — C D MARPLE *Case Rep* 240
- Coronary Occlusion, The Functional Consequences of —. C. J. WIGGERS 158
- Coronary Thrombosis, Comparative Electrocardiographic Changes in Angina Pectoris and — in the Same Patient H H ROTHENDLER *Case Rep* 268
- D**EXTROCARDIA with Situs Inversus Complicated by Chronic Rheumatic Aortic and Mitral Endocarditis G. W. PARSON *Case Rep* 102
- Digestive Glands, Secretory Mechanisms of the — B P. BABKIN *Rev* 449
- Doryl (Carbaminoylecholine), The Effect of — in the Treatment of Peripheral Vascular Disease G SALAND, R ROSENTHAL, C KILIN and H ZURROW 48
- E**LECTROCARDIOGRAPHIC Changes, Comparative — in Angina Pectoris and Coronary Thrombosis in the Same Patient H H ROTHENDLER *Case Rep* 268
- Empyema, Treatment of Postpneumonic Thoracic — with Sulfonamides, Penicillin and Repeated Thoracenteses A I JOEL, J W FRANKS and W F KAMPEL 800
- Endocarditis, Dextrocardia with Situs Inversus Complicated by Chronic Rheumatic Aortic and Mitral — G W PARSON *Case Rep* 102
- Endocarditis, Subacute Bacterial — as a Cause of Subacute Bacterial — Report of a Case Treated with Penicillin W McDONNELL, M M LEASE and M BERRY *Case Rep* 411
- Endocarditis, Treatment of Subacute Bacterial — with Penicillin Report of Cases Treated without Anticoagulant Agents J R GOERNER, A J GEIGER and F G BLAKE 491
- Equine Infectious Anemia Transmitted to Man J T PETERS *Case Rep* 271
- F**IBROSITIS, The Syndrome of Psoas Myositis and —, Its Manifestations and Its Significance in the Differential Diagnosis of Lower Abdominal Pain J A GREENE 30
- Filariasis *Edit* 1018
- Filariasis, Studies of — in Soldiers Evacuated from the South Pacific A. A GOODMAN, E M WEINBERGER, S W LIPPINCOTT, A MARBLE and W H WRIGHT 823
- Filariasis, The Early Diagnosis of — and Certain Suggestions Relative to Cause of Symptoms W E LEEDE and A I JOSEY 816
- Follicular Lymphoma (Brill-Symmers Disease) Unsuccessfully Treated with Penicillin N W DREY and F B QUEEN *Case Rep* 1009
- Fractures, Multiple — of Ribs by Cough O SWINEFORD, JR and J MCKINNON *Case Rep* 442
- G**ASTROINTESTINAL Roentgenology, The Unusual in — G M TICE 837
- Granulocytopenia (Aleukemic Leukemia), The Value of Penicillin in the Control of Sepsis Complicating a Case of Severe — V H. KUGEL and M A SCHNITZER *Case Rep* 1001
- Graves' Disease, Hyperophthalmopathy — J H MANS 711
- Graves' Disease, Observations on the Treatment of — with Thiouracil D P BARR and E. SHORR 754
- H**EART Disease, The Diagnosis of Beriberi — M A BLANKENHORN 398
- Heart Failure, Interlobar Effusion Associated with Congestive — S BOHAPAS and L. H. CHUR *Case Rep* 426
- Hemolytic Anemia, Chronic — with Paroxysmal Nocturnal Hemoglobinuria R C MANCHESTER 935

- Hemolytic Anemia, Hyperglobulinemia and Boeck's Sarcoid A R CRANE and A M ZETLIN *Case Rep* 882
- Hemopneumothorax, Spontaneous — Report of a Case Occurring in a Soldier J FRANKLIN *Case Rep* 437
- Hormones, The Chemistry and Physiology of the — F R MOULTON, Editor *Rev* 687
- Hyperglobulinemia and Boeck's Sarcoid, Hemolytic Anemia, — A R CRANE and A M ZETLIN *Case Rep* 882
- Hyperophthalmopathic Graves' Disease J H MEANS 711
- Hypersensitivity and Rheumatic Fever Part I 969  
Part II Relation of Rheumatic Fever to Hypersensitivity J K AIKAWA 983
- Hypertension Caused by Renal Infarction S BEN-ASHER *Case Rep* 431
- Hypertension, Lumbodorsal Sympathectomy for — *Edit* 108
- Hyperthyroidism and Pernicious Anemia, The Combination of — Report of a Case with a Review of the Literature F BOENHEIM, D SCHWIMMER and T H MCGAVACK *Case Rep* 869
- Hyperthyroidism, The Use of Thiouracil in the Treatment of Patients with — J L GABRILOVE, M J KERT and L J SOFFER 537
- I**DIOSYNCRATIC Febrile Reactions to Thiouracil Clinical Characteristics and Possible Pharmacologic Significance J W MCARTHUR, R W RAWSON and J H MEANS 915
- Immunity and Immunological Reactions in Mumps *Edit* 445
- Iron, Absorption and Excretion of — A G LITTLE, JR, M H POWER and E G WAKEFIELD 627
- L**EPROSY, The Classification and Nomenclature of — with Suggestions for a Simplification of Both H L ARNOLD, JR and I L TILDEN 65
- Leukemia, Aleukemic —, The Value of Penicillin in the Control of Sepsis Complicating a Case of Severe Granulocytopenia (—) V H KUGEL and M A SCHNITKER *Case Rep* 1001
- Leukopenia, Atrophic Arthritis Associated with Splenomegaly and — F N HATCH 201
- Lumbodorsal Sympathectomy for Hypertension *Edit* 108
- Lupus Erythematosus Disseminatus, Acute — A Report of a Case in a Male with Associated Atypical Verrucous Endocarditis (Libman-Sacks) S G BLOUNT, JR and J T BARRETT *Case Rep* 251
- Lymphocytosis in the Cerebrospinal Fluid I L APPLEBAUM, J SHRAGER and W PAFF 170
- Lymphoma, Follicular — (Brill-Symmers Disease) Unsuccessfully Treated with Penicillin N W DREY and F B QUEEN *Case Rep* 1009
- M**ALARIA Complicated by Pneumonia, Treatment with Sulfadiazine and Atabrine Z T BERCOVITZ *Case Rep* 79
- Medical Education in the United States before the Civil War W F NORWOOD *Rev* 893
- Medical Education, Post-War — *Edit* 890
- Mediterranean Anemia *Edit* 683
- Ménière's Disease (Hydrops of Labyrinth), Diagnosis and Surgical Treatment of — K M DAY 41
- Meningococcic Infections with Special Reference to Certain Diagnostic Considerations, An Analysis of 37 Cases A C OXMAN and I FISCHER 924
- Meningococcic Meningitis Treated with Sulfadiazine and Sulfamerazine A Three-Year Study L K SWEET, E DUMOFF-STANLEY and H F DOWLING 338
- "Metastatic" Calcification in Soft Tissues of Legs in Osteitis Deformans B SELIGMAN and L NATHANSON *Case Rep* 82
- Mononucleosis, Infectious — A Clinical Study of 63 Cases A L KRUGER, A W WALLACE and S J PENCHANSKY 945
- Mumps, Immunity and Immunological Reactions in — *Edit* 445
- Myasthenia Gravis, Familial — L MANCUSI-UNGARO *Case Rep* 249
- Myocarditis, Acute Non-Specific — S CANDEL and M C WHELOCK 309
- Myocarditis, Isolated (Fiedler's) — Report of Case First Manifested by Ar-

- terial Emboli in Extremities and Terminally by Mural Thrombi in Three of the Heart Chambers R W ROBINSON and F B QUEEN *Case Rep* 860
- Myositis, Psoas — and Fibrositis, The Syndrome of, Its Manifestations and Its Significance in the Differential Diagnosis of Lower Abdominal Pain J A GREENE 30
- NEUROPSYCHIATRIC** Complications Following Spinal Anesthesia H E YASKIN and B J ALPERS 184
- Neuroses in the Combat Zone W J BLICKWENN 177
- Neutropenia, Splenic — Report of a Case with Splenectomy W LANGSTON, O A WHITE and J D ASHLEY, JR *Case Rep* 667
- OBITUARIES**
- Baumgarten, Walter 911
- Breuer, Miles John 1041
- Burnett, Thomas Ward 1045
- Comroe, Bernard Isaac 709
- Downs, Charles McCabe 703
- Ferguson, Donald Renwick 706
- Frost, Kendal 1042
- Grill, John C 707
- Groat, William A 1044
- Hall, William Wallace 707
- Harrop, George Argale 1043
- Harvey, John Gould 912
- Hecker, Friedrich Alexander 912
- Herrick, William Worthington 306
- Inman, Jesse Headen 489
- Klaus, Emanuel 704
- Klopp, Henry Irwin 708
- Lawrence, Charles Henry 134
- Luft, Raymond 913
- Mahony, Fergus Olmsh 708
- McFarland, Joseph 913
- Mecker, George H 703
- Miner, Friedrich B 488
- Neil Frank 705
- Purdie, Robert McNair 488
- Rudy, Abraham 705
- Saxer, John Pascal 489
- Shepard, Benjamin A 911
- Sloup, Jack 1011
- Smith, Clark George 307
- Stewart, Alexander Hamilton 710
- Stewart, William S 707
- Tucker, Beverley Randolph 1045
- Welch, Paul Brown 1042
- White, Arthur Weaver 487
- Willett, Thomas 709
- Oliguria and Anuria Due to Increased Intra-renal Pressure J T PETERS 221
- Osteitis Deformans, "Metastatic" Calcification in Soft Tissues of Legs in — B SELIGMAN and L NATHANSON *Case Rep* 82
- PANCREAS**, Back Pain as a Symptom of Carcinoma of the Body of the — E E KATTWINKEL *Case Rep* 1006
- Penicillin, Follicular Lymphoma (Brill-Symmers Disease) Unsuccessfully Treated with — N W DREY and F B QUEEN *Case Rep* 1009
- Penicillin in Suppurative Disease of the Lungs Due to *Streptococcus hemolyticus* H J F KULLMAN and J A CRELLIN 135
- Penicillin, Methods of Administering — *Edit* 275
- Penicillin, Report of a Case Treated with — *Streptobacillus moniliformis* as a Cause of Subacute Bacterial Endocarditis — W McDERMOTT, M M LEASK and M BENOIT *Case Rep* 414
- Penicillin, The Use of — in Agranulocytosis R W. MOODY and S KAUVAR *Case Rep* 1015
- Penicillin, The Value of — in the Control of Sepsis Complicating a Case of Severe Granulocytopenia (Aleukemic Leukemia) V. H. KUGEL and M A SCHNITKER *Case Rep* 1001
- Penicillin Therapy Including Tyrothricin and Other Antibiotic Therapy J. A. KOLMER *Rev* 449
- Penicillin, Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, — and Repeated Thoracenteses A I JOSEY, J. W. TREVIS and W F KAMMER 800
- Penicillin, Treatment of Subacute Bacterial Endocarditis with — Report of Cases Treated without Anticoagulant Agents J R GORMAN, A J GRIGG and F. G. BLAIR 491
- Peripheral Vascular Disease, The Effect of Doryl (Carbamoylcholine) in the Treatment of — G SALAND, R ROSENTHAL, C KLEP and H ZUBROW 18

- Peritonitis, Benign Paroxysmal — S  
SIEGAL 1
- Pharmacology, Fundamentals of — C  
H THIENES *Rev* 111
- Pharmacy, American — R A LYMAN,  
Editor *Rev* 1023
- Physical Diagnosis, Aids in — Signs over  
the Lower Left Lung Caused Chiefly by  
Cardiac Enlargement E M CHAP-  
MAN and R G ANDERSON 35
- Physical Foundations of Radiology O  
GLASSER, E H QUIMBY, L S TAYLOR  
and J L WEATHERWAX *Rev* 111
- Pneumonia, Malaria Complicated by —,  
Treatment with Sulfadiazine and Ata-  
brine Z T BERCOVITZ *Case Rep* 79
- Polyneuritis, Acute Infectious — (Guil-  
lain-Barré Type) J G CHUSID and  
G H MARQUARDT 852
- Post-War Medical Education *Edit* 890
- Pulmonary Actinomycosis Due to *Actino-  
myces graminis* J P LYNCH and R A  
HOLT *Case Rep* 91
- Q**UINIDINE, Ventricular Tachycar-  
dia — A Report of 10 Cases, Eight  
of Which Were Treated with —  
with Recovery in Seven S L ZIV-  
MERMAN 634
- R**ABIES Problem, A Current View of  
the — J CASALS 74
- Radiologic Examination of the Small In-  
testine R GOLDEN *Rev* 280
- Radiology, Physical Foundations of —  
O GLASSER, E H QUIMBY, L S  
TAYLOR and J L WEATHERWAX *Rev* 111
- Reiter's Disease, A Syndrome Termed —  
(Urethritis, Conjunctivitis and Arthri-  
tis) C D MILLER and D W MC-  
INTYRE *Case Rep* 673
- Renal Failure, Tissue Calcification and —  
Produced by Massive Dose Vitamin D  
Therapy of Arthritis T S DANOW-  
SKI, A W WINKLER and J P PETERS 22
- Renal Infarction, Hypertension Caused  
by — S BEN-ASHER *Case Rep* 431
- Respiratory Infections, Upper — A Ré-  
sume of Recent Pertinent Data and  
Observations of Incidence Aboard a  
Destroyer W H HARRIS, JR 147
- Rheumatic Aortic and Mitral Endocardit-  
is, Dextrocardia with Situs Inversus  
Complicated by Chronic — G W  
PARSON *Case Rep* 102
- Rheumatic Fever, Hypersensitivity and  
— Part I 969  
Part II Relation of Rheumatic Fever  
to Hypersensitivity J K AIKAWA 983
- Roentgenology, The Unusual in Gastro-  
intestinal — G M TICE 837
- Rothmund's Syndrome, Werner's Syn-  
drome (Progeria of the Adult) and —,  
Two Types of Closely Related Heredo-  
familial Atrophic Dermatoses with Ju-  
venile Cataracts and Endocrine Fea-  
tures, A Critical Study with Five New  
Cases S J THANNHAUSER 559
- S**ARCOID, Hemolytic Anemia, Hyper-  
globulinemia and Boeck's — A R  
CRANE and A M ZETLIN *Case Rep* 882
- Savill's System of Clinical Medicine Deal-  
ing with the Diagnosis, Prognosis, and  
Treatment of Disease for Students and  
Practitioners E C WARNER, Editor  
*Rev* 280
- Secretory Mechanisms of the Digestive  
Glands B P BABKIN *Rev* 449
- Sickle Cell Disease, The Pathology of —  
R C MURPHY, JR and S SHAPIRO 376
- Splenic Neutropenia Report of a Case  
with Splenectomy W LANGSTON, O  
A WHITE and J D ASHLEY, JR *Case  
Rep* 667
- Splenomegaly and Leukopenia, Atrophic  
Arthritis Associated with — F N  
HATCH 201
- Streptobacillus moniliformis* as a Cause of  
Subacute Bacterial Endocarditis Re-  
port of a Case Treated with Penicillin  
W McDERMOTT, M M LEASK and  
M BENOIT *Case Rep* 414
- Streptococcus hemolyticus*, Penicillin in  
Suppurative Disease of the Lungs Due  
to — H J F KULLMAN and J A  
CRELLIN 135
- Sulfadiazine and Atabrine, Treatment  
with — Malaria Complicated by  
Pneumonia — Z T BERCOVITZ  
*Case Rep* 79
- Sulfadiazine and Sulfamerazine, Men-  
ingococcal Meningitis Treated with —  
A Three-Year Study L K SWEET,  
C DUMOFF-STANLEY and H F DOW-  
LING 338
- Sulfathiazole, Thrombocytopenic Pur-  
pura Following the Use of — P S

- STRONG and E M GLASSBURN *Case Rep* 237
- Sulfonamides, Treatment of Postpneumonic Thoracic Empyema with —, Penicillin and Repeated Thoracenteses A I JOSEY, J W TREVIS and W F KAMMER 800
- Sympathectomy, Lumbodorsal — for Hypertension *Edit* 108
- T**HIOURACIL, Idiosyncratic Febrile Reactions to — Clinical Characteristics and Possible Pharmacologic Significance J W McARTHUR, R W RAWSON and J H. MEANS 915
- Thiouracil, Observations on the Treatment of Graves' Disease with — D P BARR and E SHORR 754
- Thiouracil, The Effects of — on the Thyroid Gland J W SHIRER and M COHEN 790
- Thiouracil, The Use of — in the Treatment of Patients with Hyperthyroidism J L GABRIOVE, M J KERT and L J SORFER 537
- Thoracenteses, Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, Penicillin and Repeated — A I JOSEY, J W TREVIS and W F KAMMER 800
- Thrombocytopenic Purpura Following the Use of Sulfathiazole P S STRONG and E M GLASSBURN *Case Rep* 237
- Thyroid Gland, The Effects of Thiouracil on the — J W SHIRER and M COHEN 790
- Tissue Calcification and Renal Failure Produced by Massive Dose Vitamin D Therapy of Arthritis T S DANOWSKI, A W WINKLER and J P PETERS 22
- Typhus Fever, Azotemia in — A YEOMANS, J C SNYDER, E S MURRAY, R S ECKE and C J D ZARAFONETIS 711
- Typhus Fever, Endemic (Murine) — Clinical Observations of 180 Cases B M STUART and R L PULLEN 520
- Tyrothricin and Other Antibiotic Therapy, Penicillin Therapy Including — J A KOLMER *Rev* 449
- V**ASCULAR Disease, The Effect of Doryl (Carbaminoylcholine) in the Treatment of Peripheral — G SALLAND, R ROSENTHAL, C KLEIN and H. ZURROW 48
- Ventricular Tachycardia — A Report of 10 Cases, Eight of Which Were Treated with Quinidine with Recovery in Seven S L ZIMMERMAN 634
- Vitamin D Therapy of Arthritis, Tissue Calcification and Renal Failure Produced by Massive Dose — T S DANOWSKI, A W WINKLER and J P PETERS 22
- W**ERNER'S Syndrome (Progeria of the Adult) and Rothmund's Syndrome; Two Types of Closely Related Heredofamilial Atrophic Dermatoses with Juvenile Cataracts and Endocrine Features, A Critical Study with Five New Cases S J THANNHAUSER 559

